TABLE 8.9.4.3.1		
COSTART body system	**Sibutramine**	**Placebo**
Digestive	49	59
Heme and lymphatic	2	7
Metabolic and nutritional	23	16
Musculoskeletal	15	18
Nervous	45	34
Respiratory	21	16
Skin and appendages	19	16
Special senses	9	7
Urogenital	26	18
Overall	96	95

Test of proportions of patients reporting: $\chi^2=0.01$, $p=0.95$

The most common adverse events; reported by more than 5% of patients are summarized in table 8.9.4.3.2

Table 8.9.4.3.2		
COSTART term	**Placebo**	**Sibutramine**
Asthenia	5	2
Flu syndrome	5	1
Headache	19	14
Infection	1	8
Abdominal pain	3	5
Back pain	4	5
Chest pain	4	3
Constipation	13	13
Diarrhea	6	4
Dyspepsia	2	5
Flatulence	6	3
Hyperglycemia	3	5

Table 8.9.4.3.2		
COSTART term	**Placebo**	**Sibutramine**
Hypoglycemia	5	1
Arthralgia	4	4
Dizziness	6	6
Dry mouth	5	10
Paresthesia	3	2
Pharyngitis	4	8
Sweatiness	2	4
Albuminuria	3	3

The increased number of infections reported in the sibutramine group represent upper respiratory tract infections and may be related to the drug-induced xerostomia.

Four patients experienced serious or potentially serious adverse events (one in placebo and 3 in sibutramine). A 49 year old female in the placebo group entered the hospital for endoscopy after 36 days into the study. A 52 year old female in the sibutramine group was hospitalized for arthroscopy of the knee after 83 days of treatment. A 65 year old female in the sibutramine group was hospitalized for varicose vein surgery after 50 days of treatment. And a 60 year old black female experienced deterioration in renal function after 46 days of sibutramine treatment this was felt to be possibly due to the initiation of diuretic therapy during the study.

Five patients (two in the placebo group and 3 in the sibutramine group) withdrew from the study because of an adverse event. One of the placebo patients withdrew because of moderate giddiness and vomiting and the other subject withdrew because of a severe headache. The sibutramine subjects withdrew because of moderate dizziness, moderate insomnia, and moderate diarrhea, respectively.

Clinical chemistries

The difference between the two groups for the change from baseline to endpoint was statistically significant for packed cell volume, mean cell volume, and platelets. However, none of these changes appeared to be clinically significant.

Lipoprotein lipids

In the sibutramine group there were small, non-significant mean reductions in triglyceride, total cholesterol, and VLDL levels compared with small increases in the placebo group. In addition,

there was a small mean increase in HDL-C levels in the sibutramine group compared with no change in the placebo group. The levels of LDL-C increased slightly in both groups.

Vital signs

The changes in vital signs from baseline to week 12 for completers are provided in table 8.9.4.3.2

TABLE 8.9.4.3.2		
	Sibutramine n=43	**Placebo n=40**
Systolic blood pressure	-0.2	-0.2
Diastolic blood pressure	3.0	2.5
Pulse	7.5*	0.2

*p=0.005 compared to placebo; blood pressure in mmHg and pulse in beats per minute

Electrocardiograms

The mean change from baseline to endpoint in heart rate from ECG was 9.1 and -4.8 ($p<0.001$) in the sibutramine and placebo groups, respectively The only other ECG parameter that was statistically different between the two groups was the QT interval. There was a mean increase of 2.8 ms in the placebo groups and a mean decrease of 14.8 ms in the sibutramine group ($p=0.002$).

CONCLUSIONS

8.9.5 In this 12-week study of obese NIDDM patients, 15 mg QD of sibutramine resulted in a small, but statistically significant reduction in body weight and percent body fat when compared to placebo. However, despite a mean reduction in body weight of 2.3 kg, $HbA1_c$ levels did not change significantly in the sibutramine-treated patients. Whereas systolic blood pressure did not change in either group, diastolic blood pressure increased slightly in each group and there was a statistically significant increase in the pulse rate in the sibutramine group. The clinical significance of this moderate increase in pulse, if sustained with long-term use of sibutramine, is unknown. There were small, favorable, but non-statistically significant changes in lipid profiles in the sibutramine group.

8.10 SB 3068

OBJECTIVE/RATIONALE

8.10.1 The objective of this study was to evaluate the efficacy and tolerability of 15 mg QD of sibutramine in obese type II diabetic patients who completed the 12-week core study SB 3051.

This open-label extension study was conducted for 12 weeks.

DESIGN

8.10.2 This was a 2-center, open, non-comparative extension trial to examine the long-term efficacy and tolerability of sibutramine 15 mg QD in the treatment of obese patients with type II diabetes who completed the core study SB 3051. Subjects who received placebo during the core study received 15 mg QD of sibutramine during the extension study. Each patient was interviewed by a dietitian and was encouraged to follow specific dietary recommendations for diabetics. Assessments were made at weeks 16, 20, 24, and at 4-weeks post-active treatment.

PROTOCOL

POPULATION

8.10.3.1 Upon completion of the double-blind, placebo-controlled, parallel-group core trial, SB 3051, patients were assessed for eligibility to continue into this extension trial. Eligible patients were of either sex, and between [redacted] years of age. Patients were not eligible to participate in the extension trial if they had a diastolic blood pressure greater than 110 mmHg or experienced a serious adverse event during the core trial.

ENDPOINTS

8.10.3.2 The primary endpoints of this extension study included change in body weight, waist and hip circumferences, body composition (DEXA), and blood pressure and pulse. A test meal with measurement of glucose and insulin concentrations was also an endpoint measured at week 24. The change in $HbA1_c$ levels was assessed at weeks 12 and 24. Changes in diabetic medication were also recorded.

STATISTICAL CONSIDERATIONS

8.10.3.3 The change in body weight, calculated on a last observation carried forward basis, from week 0 to week 24 for the group randomized to receive sibutramine in the core study (SB3051) and the corresponding changes from week 12 to week 24 within each group from SB 3051 were reported with 95% confidence intervals. One-way ANOVA with a factor for center was conducted to evaluate for consistency of any treatment effect between the two centers. It was not possible to accurately calculate the statistical power of the extension trial because it was unknown how many subjects would complete the core study. The changes in fasting glucose and insulin levels during the core trial did not follow a normal distribution, and therefore, the Hodges-Lehmann estimate of the median changes and the associated 95% confidence intervals were reported. Fasting insulin levels recorded below the detection range of the assay were reset to the lower assay limit, similarly, any value recorded above the detection range was reset to the upper detection limit. Changes in fasting insulin concentrations were analyzed for subgroups of

patients, as defined by the concomitant diabetic medication.

RESULTS

POPULATION ENROLLED/ANALYZED

8.10.4.1 A total of 74 patients completed the core trial and continued into the extension trial. Of these, 67 patients completed the extension trial. Table 8.104.1.1 provides the baseline (week 12) characteristics of the two groups from the core study.

TABLE 8.10.4.1.1

Variable	Sibutramine n=37	Placebo n=37
Age (yrs)	53.3	54.5
Male	19	17
Female	18	20
Weight (kg)+	81.8	83.9
BMI (kg/m^2)	29.5	31.0

+ median values

As expected, the individuals who received sibutramine in the core study weighed less than those who received placebo. This difference in body weight was more pronounced for the males (median weight 82.6 vs 87.7 kg for sibutramine vs placebo, respectively).

EFFICACY ENDPOINT OUTCOMES

Body weight

8.10.4.2 The mean actual change in body weight (kg) to endpoint for the groups by original treatment in the core study are shown in table 8.10.4.2.1

TABLE 8.10.4.2.1

Previous tx	n	Change from wk 12	95% CI	n	Change from wk 0	95% CI
Sib 15 mg	36	-0.6 kg	-1.2,0.0 kg	36	-3.3 kg	-4.2,-2.3 kg
Placebo	37	-1.9 kg	-2.6,-1.3 kg	37	-2.5 kg	-3.3,-1.7 kg

It should be noted that the absolute weight loss in the diabetics who received 15 mg QD of sibutramine from baseline to endpoint was a modest 3.3 kg.

Table 8.10.4.2.2 illustrates the mean percentage change in body weight to endpoint.

TABLE 8.10.4.2.2						
Previous tx	**n**	**Change from wk 12**	**95% CI**	**n**	**Change from wk 0**	**95% CI**
Sib 15 mg	36	-0.7%	-1.4, 0.0	36	-3.8%	-4.9, -2.8
Placebo	37	-2.3%	-3.1, -1.5	37	-3.0%	-3.9, -2.1

The results of the mean percentage change in body weight were similar for the completers dataset, and again, indicate that sibutramine caused a modest, but statistically significant reduction in percent body weight when administered for 24 weeks.

Body composition

The sibutramine group had a statistically significant reduction in waist circumference, whereas the placebo group did not. The change in waist circumference for the sibutramine group from week 0 to week 24 was -4.7 cm (95% CI -2.7, -6.6 cm).

The changes from week 0 to endpoint in body composition measured by DEXA are shown in table 8.10.4.2.3

TABLE 8.10.4.2.3		
Body Component	**Sibutramine n=34**	**Placebo n=34**
Soft tissue mass (kg)	-3.2 (-4.2, -2.2)	-2.4 (-3.2, -1.5)
Fat mass (kg)	-2.7 (-3.6, -1.8)	-1.8 (-2.6, -1.1)
Lean mass (kg)	-0.5 (-1.1, 0.0)	-0.5 (-1.0, -0.1)
Percentage fat mass (%)	-1.9 (-2.7, -1.1)	-1.1 (-1.7, -0.5)
Bone mineral content (g)	-15.1 (-42.6, 12.5)	-8.3 (-23.9, 7.3)

Values in parentheses represent the 95% CI

There were statistically significant reductions in fat mass and percentage fat mass in both groups. There was also a small reduction in lean mass in both groups; this reduction was statistically significant in the placebo group only.

Metabolic control

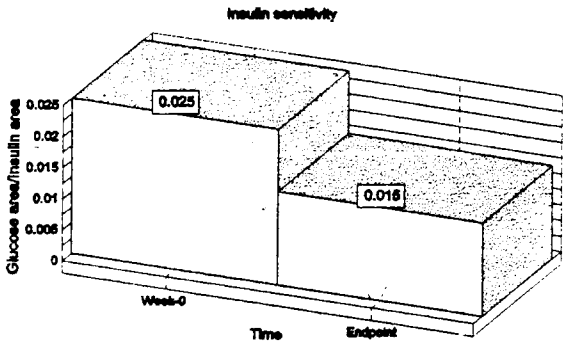
There were no statistically or clinically significant changes in fasting glucose or insulin levels during the extension study. Similarly, there were no significant changes in the levels of $HbA1_c$ in either group (95% CI for the change from week 0 to week 24: -0.5, 0.5% for the sibutramine

group and -0.2, 0.5% for the placebo group).

In general there were no significant changes in the fasting or post-test meal glucose concentrations in the sibutramine or placebo groups at endpoint. However, there was a statistically significant increase in the incremental AUC for insulin following a test meal in the sibutramine group from week 0 to endpoint (8.5 mmol/l.min) and week 12 to endpoint (12.3 mmol/l.min). The increase in insulin levels following treatment with sibutramine without a significant reduction in glucose concentrations raises the possibility that sibutramine treatment was associated with a decrease in insulin sensitivity.

The ratio of glucose to insulin concentration is a crude index of insulin sensitivity. Figure 8.10.4.2.1 illustrates the change in the ratio of the glucose to insulin area following a test meal in the sibutramine group. The decrease in the ratio of glucose to insulin again suggests a possible reduction in insulin sensitivity. The effect of sibutramine-induced weight loss on insulin sensitivity should be definitively examined by the hyperinsulinemic and hyperglycemic clamp techniques.

Figure 8.10.4.2.1



Subgroup analysis

Whereas, overall, there was no change in the mean $HbA1_c$ concentration in the sibutramine-treated subjects, the Sponsor reported that 13 subjects who were randomized to sibutramine treatment in the core study SB 3051 had reductions in $HbA1_c$ of > than 1.0%.

Table 8.10.4.2.4 provides the metabolic responses of the 13 subjects who had a favorable decrease in $HbA1_c$ levels.

TABLE 8.10.4.2.4								
#subjects	**Δ Weight**	**Δ G_0**	**Δ I_0**	**ΔG AUC**	**Δ I AUC**	**Δ SBP**	**Δ DBP**	**Δ P**
13	-4.5	-2.6	0.7	-0.17	9.1	-0.8	1.6	6.5

Deltas represent the change from baseline to endpoint.
Δ Weight in kg; **Δ G_0** = change in fasting glucose level in mmol/l; **Δ I_0** = change in fasting insulin level in U/l; **ΔG AUC** = change in incremental area under the curve post-test meal for glucose in mol.l/min; **ΔI AUC** = change in incremental area under the curve post-test meal for insulin in mmol.l/min; **ΔSBP** = change in systolic blood pressure in mmHg; **ΔDBP** = change in diastolic blood pressure in mmHg; **ΔP** = change in pulse in beats per minute.

The metabolic responses in this subgroup of subjects who had a reduction in $HbA1_c$ of >1% were similar to those of the overall group, and indicate that post-load insulin levels increased, as did diastolic blood pressure and pulse rate following treatment with sibutramine. In sum, in this subgroup of patients, the favorable reduction in $HbA1_c$ levels was not accompanied by favorable changes in other metabolic or co-morbid conditions.

Change in antidiabetic medication

The changes in anti-diabetic therapy during the extension study categorized by treatment group in the core study are illustrated in table 8.10.4.1.2

TABLE 8.10.4.1.2						
Therapy	**Reduction in dose**		**Increase in dose**		**No change in dose**	
	Sib	Pl	Sib	Pl	Sib	Pl
Insulin	1	3	4	1	5	5
Sulphonyl	1	2	0	2	17	9
Metformin	0	0	0	0	8	14

It appears that more sibutramine-treated patients had an increase in their insulin dose than did placebo patients.

SAFETY OUTCOMES

APPEARS THIS WAY
ON ORIGINAL

Adverse events

8.10.4.3 Adverse experience data are available for 73/74 subjects. The most common events were in the COSTART categories Body as a Whole, Digestive and Nervous Systems. The adverse events reported by greater than 5% of patients who received sibutramine are listed in table 8.10.4.3.1

TABLE 8.10.4.3.1			
COSTART term	**Placebo**	**Sibutramine❁**	
	Weeks 12-24	**Weeks 12-24**	**Weeks 0-24**
Asthenia	4	1	2
Headache	8	4	9
Infection	1	-	9
Pain	5	1	2
Abdominal pain	3	1	1
Back pain	-	-	4
Chest pain	3	3	4
Palpitation	2	-	2
Constipation	8	4	17
Dyspepsia	1	2	4
Nausea	3	-	2
Hyperglycemia	-	3	6
Hypoglycemia	3	1	2
Arthralgia	1	3	6
Dizziness	4	4	9
Dry mouth	10	4	14
Insomnia	2	3	3
Pharyngitis	7	3	8
Sweat	2	2	7
Albuminuria	1	-	3

❁ includes adverse events reported in core trial

Two patients experienced serious adverse events. Both patients remained in the study. One patient, a 63 year old Black male, experienced mild chest pain following a fall in which his chest was injured. Angina was diagnosed by an exercise treadmill test; the patient did complete the study. The second patient, a 51 year old Caucasian male, was hospitalized for left knee arthroscopy. One patient started an antidepressant because of mild depression.

Six patients withdrew from the study because of an adverse event. These are summarized in table 8.10.4.3.2

TABLE 8.10.4.3.2						
Number	**Age**	**Gender**	**Dose**	**Duration**	**Event**	**Comment**
44	54	M	15	105	severe abdominal pain	dx with constipation
70	55	F	15	93	worsening of diabetes	FBS of 23.4 mmol/l
71	58	M	15	105	severe hyperlipidemia IIB	cholesterol and TG levels rose significantly during the trial and decreased after drug stopped
76	44	M	15	163	⇑ LFTs	? relationship to drug
104	41	M	15	121	mild hyperglycemia	possible relationship to drug
115	54	F	15	5	headache	persisted 82 days post-withdrawal

Clinical chemistries

There were two potentially significant clinical laboratory value changes during the study. One patient was receiving iron treatment for anemia. During the course of the core and extension studies her hemoglobin level decreased from 11.3 g/dl to 9.7 g/dl. No results were available from week 28. Another patient had an increase in urea and creatine levels at week 24 (9.3 mmol/l and 203 umol/l, respectively. The values returned to normal at the end of the study.

Lipoprotein lipids

There were no statistically significant changes in lipoprotein lipid levels in the group that received sibutramine in the core study and completed the 24 week extension study.

Vital signs

Table 8.10.4.3.3 illustrates the mean changes in blood pressure and pulse.

TABLE 8.10.4.3.3		
Variable	**Mean change (95% CI) by previous treatment in core study**	
	Placebo (week 12-24)	**Sibutramine (week 0-24)**
	n=34	n=33
Systolic BP (mmHg)	5.1	0.8
Diastolic BP (mmHg)	2.8	3.6
Pulse rate (bpm)	6.6	10.1

❁ statistically significant, $p<0.05$

As shown in the above table there were statistically significant increases in diastolic blood pressure and pulse rate in the patients who received sibutramine from week 0 to week 24.

Electrocardiograms

Aside from a mean increase in heart rate of 8 to 9 beats per minute, there were no clinically significant changes in the ECGs.

8.10.5 SPONSOR'S CONCLUSIONS

"Treatment with sibutramine 15 mg once-daily, for up to six months produced sustained weight loss in this type II diabetic patient population. Sibutramine did not appear to affect diabetic control or the management of these patients. From the first dose of sibutramine, there was a mean increase in heart rate during the initial 12 weeks of sibutramine treatment; those patients who received an additional 12 weeks of treatment had little further change in heart rate. Sibutramine was well tolerated for up to six months in this patient population."

8.10.6 MEDICAL OFFICER'S SUMMARY AND CONCLUSIONS

This Reviewer does not agree with the Sponsor's conclusions that sibutramine was well tolerated in this diabetic population. The rationale for this statement is as follows: In this 12 week open-label extension study of obese type II diabetics, 15 mg QD of sibutramine produced minimal to modest reductions in body weight and percent body fat. Despite a 3.3 kg reduction in weight, there were no improvements in glucose metabolism as assessed by $HbA1_c$ concentrations, and fasting and post-load glucose concentrations. Moreover, the data suggest the possibility of reduced insulin sensitivity following treatment with sibutramine, as the AUC for insulin following a test meal increased without a significant reduction in glucose levels in the drug-treated group. This issue should be further explored with more sensitive methodologies such as the hyperglycemic and hyperinsulinemic clamps.

Regarding other co-morbid conditions, 24-weeks of treatment with sibutramine increased diastolic blood pressure and pulse rate and did not improve lipoprotein lipid levels.

HYPERTENSION

8.11 BPI 855

APPEARS THIS WAY
ON ORIGINAL

OBJECTIVE/RATIONALE

8.11.1 The objective of this study was to assess the effects of 20 mg QD of sibutramine on blood pressure as measured by 24-hour ambulatory monitoring in obese, hypertensive patients

controlled by a single antihypertensive agent.

DESIGN

8.11.2 This study was a single center, parallel-group, double-blind, fixed-flexible dose, placebo-controlled study of 20 patients (10 sibutramine and 10 placebo). Following a 7-day inpatient phase during which time the subjects received sibutramine or placebo starting on day 1, the subjects were discharged and continued their dosing for an additional 7 weeks. During the outpatient phase, the subjects were allowed to reduce their dose from 20 mg QD to 10 mg QD if they developed intolerable side effects. Assessments were conducted at weeks 2, 4, 6, 8, and 9.

PROTOCOL

POPULATION

8.11.3.1 Inclusion criteria:
1. Male or female patients between the ages of_____ years.
2. Body weight between
3. Documented history of essential hypertension (untreated diastolic blood pressure greater than 90 mmHg), or hypertension treated for at least 6 weeks prior to screening with the same dose of a single antihypertensive agent (calcium channel blocker, ACE inhibitor, or diuretic), and have a supine diastolic blood pressure of 95 mmHg or less on 2 successive occasions.

Exclusion criteria:
1. Thyroid hormone replacement therapy, beta-blockers, centrally acting sympathetic agents, alpha-2-agonists, and ganglionic blocking agents.

ENDPOINTS

8.11.3.2 Twenty-four hour ambulatory blood pressure monitoring (ABPM) was performed during screening, inpatient day 0, inpatient day 3, outpatient week 4, and outpatient week 8. In addition to the standard laboratory measurements, the patients had measurements for 24-hour urinary VMA, plasma catecholamines, and plasma drug levels. Changes in vital signs, Appetite scales, and the Modified Norris Assessment scores were measured. During the screening phase patients recorded food intake for 4 days and received counseling from a dietitian to ensure intake of appropriate calories so that **weight loss would be minimized** and the effects of the drug on blood pressure would not be confounded by weight loss.

STATISTICAL CONSIDERATIONS

8.11.3.3 The study report states that all comparisons between groups were conducted with t-tests. There is no mention of correction for multiple t-tests. The descriptive statistics for the observed body weights and their change from baseline were calculated and one-way ANOVAs

performed for the changes from baseline values, by visit. A repeated-measures ANOVA was performed for the changes from baseline values; the factors were visit, treatment, treatment by visit interaction, and patient within treatment. Because of the sizable treatment difference with respect to weight at baseline, analyses of covariance were completed for weight change, by visit. The factors in the ANCOVAs were treatment and baseline weight. Fisher's Exact Test was performed to determine whether or not there were treatment differences with respect to the number of patients reporting adverse experiences during the study.

RESULTS

POPULATIONS ENROLLED/ANALYZED

8.11.4.1 Twenty patients were enrolled in the study and 19 completed the study. Subject # 18 in the sibutramine group withdrew from the study after 4 weeks because of fatigue, dry mouth, and increased perspiration.

Table 8.11.4.1.1 provides the baseline demographic information for the two groups.

TABLE 8.11.4.1.1

Demographic Characteristic	Placebo n=10	Sibutramine n=10
Age (yrs)	51.8 ± 6.7	49.9 ± 5.9
Weight (kg)	105.6 ± 18.5	93.5 ± 11.5
Male	4	0
Female	6	10
Black	4	5
Caucasian	6	5
Supine systolic blood pressure (mmHg)	131.0 ± 11.9	127.8 ± 13.4
Supine diastolic blood pressure (mmHg)	83.8 ± 8.0	81.0 ± 5.8
Supine pulse rate (bpm)	77.6 ± 8.0	78.4 ± 5.1

Values are means ± SD

There were significant differences between the two groups with respect to baseline sex distribution (p=0.04) and near significant differences with respect to baseline body weight (p=0.10). The calculated BMIs for the placebo and sibutramine groups are 41.4 kg/m^2 and 32.5 kg/m^2.

Table 8.11.4.1.2 summarizes the concurrent antihypertensive therapy for the two groups at baseline.

TABLE 8.11.4.1.2			
Anti-hypertensive agent	**Dose range**	**Placebo**	**Sibutramine**
Calcium Channel Blocker	5-180 mg	2	2
Diltiazem		1	0
Isradipine		1	1
Nifedipine —		0	1
ACE inhibitor	5-10 mg	1	1
Enalapril		1	1
ACE Inhibitor + diuretic	unknown	2	0
Captopril + hydrochlorothiazide		1	0
Enalapril + hydrochlorothiazide		1	0
Diuretic	25-100 mg	5	7
Furosemide		1	0
Hydrochlorothiazide		1	3
Spironolactone		1	0
Triamterene + hydrochlorothiazide		2	4

The anti-hypertensive treatments were similar for the two groups.

EFFICACY ENDPOINT OUTCOMES

8.11.4.2 Weight loss was not an intended outcome of this study; and although there was a small mean reduction in body weight in the sibutramine group (-1.7 kg) and a small increase in the placebo group (0.2 kg) the difference was not statistically significant. The ANCOVA analysis results were the same as the ANOVA assessment and confirmed that there were no significant differences between the two groups.

SAFETY OUTCOMES

Blood pressure

8.11.4.3 The following tables illustrate the time points at which there were significant or nearly significant ($0.1>p>0.5$) treatment differences for the change in blood pressure from baseline as measured by 24-hour ambulatory monitoring.

TABLE 8.11.4.2.1			
24-Hour Ambulatory Systolic Blood Pressure Change from baseline (mmHg)			
Time Point	Placebo	Sibutramine	p-value
Day 3/Hour 24	0.7	-15.4	0.08
Week 4/Hour 2	-9.0	13.2	0.09
/Hour 12	-24.8	3.0	0.08
/Hour 16	-29.2	8.9	0.04
Week 8/Hour 16	-30.2	13.4	0.05

TABLE 8.11.4.2.2			
24-Hour Ambulatory Diastolic Blood Pressure Change from baseline (mmHg)			
Time Point	Placebo	Sibutramine	P-value
Day 3/Hour 16	0.0	9.4	0.02
Week 4/Hour 2	-12.5	4.3	0.03
/Hour 16	-16.2	10.0	0.0001
/Hour 20	-6.7	3.9	0.09
/Hour 24	-21.5	3.9	0.08
Week 4/Overall	-8.0	2.2	0.03
Week 8/Hour 4	-9.0	4.3	0.05
/Hour 16	-14.8	7.5	0.004
/Hour 20	-17.9	7.8	0.06
/Hour 24	-38.9	1.9	0.08
Week 8/Overall	-7.7	3.7	0.04

TABLE 8.11.4.2.3			
24-Hour Ambulatory Mean Arterial Pressure Change from baseline			
Time Point	Placebo	Sibutramine	p-value
Week 4/Hour 2	-11.3	7.2	0.04
/Hour 12	-15.4	-0.9	0.09
/Hour 16	-20.5	9.6	0.0004
Week 4/Overall	-8.7	2.6	0.07
Week 8/Hour 4	-7.1	5.8	0.06
/Hour 16	-20.0	9.5	0.009
/Hour 20	-16.0	9.8	0.07
Week 8/Overall	-5.6	5.5	0.10

It is clear from the above data that treatment with sibutramine was associated with elevations in blood pressure when compared to the blood pressure response in the placebo subjects.

It is interesting and important to note that there were statistically and clinically significant increases in mean arterial blood pressure in the sibutramine group during the hours 10:00 pm to 6:00 am for week 4 (-14 vs 4.0 mmHg; placebo vs sibutramine, $p<0.05$) and week 8 (-16.0 vs 8.0 mmHg, $p<0.05$).

Blood pressure was also measured with a sphygmomanometer and no significant differences were noted between the two groups. A repeated measures ANOVA did not reveal any statistically significant differences between the two groups for any of the manually-measured blood pressure parameters.

In general, heart rates were increased above baseline in both treatment groups at all times. Table 8.11.4.2.4 illustrates the time points for the significant or nearly significant treatment differences for the change in pulse rate from baseline.

TABLE 8.11.4.2.4

24-Hour Ambulatory Heart Rate Change from baseline (bpm)

Time Period	Placebo	Sibutramine	p-value
Day 3/Hour 16	2.4	7.5	0.08
/Hour 20	-3.7	4.5	0.01
Week 4/Hour 24	-1.1	10.9	0.1
Week 8 /Hour 1	4.1	23.0	0.02
/Hour 3	3.4	25.8	0.02
/Hour 4	5.7	16.9	0.006
/Hour 5	5.7	22.9	0.003
/Hour 12	-2.0	10.7	0.07
/Hour 24	-3.4	12.7	0.004
Overall	3.5	15.1	0.01

Adverse events

The most commonly reported adverse events were headache (7 in sibutramine and 4 in placebo), infection (3 in sibutramine and 4 in placebo), constipation (4 in sibutramine and 2 in placebo), and anorexia (3 in sibutramine and 3 in placebo). There were no statistically significant differences between the two groups with respect to incidence of reported adverse events.

Clinical chemistries

There were no significant changes in hematology parameters noted during the study. There were also no clinically significant changes in serum chemistry values during the study. There were no significant changes in urinary VMA concentrations in the two groups. The treatments did not have any effect on thyroid function parameters.

Lipoprotein lipids

The changes in lipoprotein lipid levels were minor and similar in the two groups.

Plasma catecholamine levels

The plasma norepinephrine level increased in the placebo group (62.8 pg/ml) and in the sibutramine group (18.4 pg/ml). The numbers of measurements of epinephrine and dopamine were insufficient to make comparisons.

Electrocardiograms

In general, there were nonsignificant differences in ECG parameters, including heart rate, PVCs and PACs between the two groups.

Appetite and Mood assessment

The two groups did not differ with respect to components of appetite. No differences in compliance were observed (except week 8); the distribution of successful and unsuccessful dietary compliance across the treatment groups was almost identical. There were no clear differences between the two groups with respect to mood as assessed by the Modified Norris Assessment with the exception of alertness, excitement, and energy, which showed favorable trends in the sibutramine group.

8.11.5 SPONSOR'S CONCLUSIONS

"In general, few significant treatment differences were demonstrated in this small pilot study comparing the effect of sibutramine vs. placebo in a population of obese hypertensive patients whose hypertension was adequately controlled by available oral agents, although modest increases in heart rate and nocturnal blood pressure were apparent.

Sibutramine 20 mg daily appeared to be well tolerated and did not affect the frequency of adverse experiences. Laboratory values, vital signs, ECG measurements, and physical examination parameters appeared to be similar for the sibutramine and placebo groups."

8.11.6 MEDICAL OFFICER'S CONCLUSIONS

Although this study was conducted in a small number of hypertensive subjects it is a valuable

study because of the use of 24-hour ambulatory blood pressure monitoring, a technique that reduces measurement error and provides an integrated assessment of blood pressure.

This Reviewer does not agree with the Sponsor's statement that "**modest** increases in heart rate and nocturnal blood pressure were apparent." While manually-measured blood pressures were not statistically significantly different between the sibutramine and placebo groups, the 24-hour ambulatory blood pressure data indicated that the use of sibutramine significantly increased blood pressure and pulse. In particular, nocturnal blood pressure tended to be higher in the sibutramine group compared to the placebo group.

There were two disconcerting findings from this study. The first is the paradoxical increase in nocturnal blood pressure in the sibutramine-treated subjects. The second is the discrepancy between the results obtained by 24-hour ambulatory blood pressure monitoring with the results from the manually-measured blood pressures. Collectively, the results of this study suggests that 24-hour ambulatory blood pressure monitoring should be used in a larger group of hypertensive patients in which weight loss is a therapeutic goal.

8.12 SB 2057

OBJECTIVE/RATIONALE

8.12.1 The objectives of this study included comparing the efficacy, safety, and tolerability of 10 mg QD of sibutramine to placebo in obese, hypertensive patients for 12 weeks. An additional objective was to assess the effect of sibutramine-induced weight loss on blood pressure.

DESIGN

8.12.2 This study was a double-blind, parallel-group, placebo-controlled 12 week study of 113 patients. There was a 3-week washout period during which time patients received dietary advice. Subjects were randomized to 10 mg QD of sibutramine or placebo (taken in the morning) for 12 weeks and then followed-up for one month following cessation of therapy.

PROTOCOL

POPULATION

8.12.3.1 Inclusion criteria included:

1. Male or female patients
2. Age
3. BMI of
4. Resting diastolic blood pressure within the range mmHg; during the screening phase blood pressure was measured in the supine and standing positions and 3 measurements were taken.

5. The use of antihypertensive medication was allowed. Subjects were allowed to take 2 antihypertensive agents if the dosage had been maintained for a minimum of 4 weeks prior to screening.

ENDPOINTS

8.12.3.2 Endpoints included change in body weight, waist and hip circumferences, diastolic and systolic blood pressure (measured 3 times while subjects were supine and standing) and heart rate. The change in Clinical Global Impression Scale, change in use of tobacco and alcohol, change in dietary compliance and hunger, satiety, appetite, craving and snacking scales were also assessed.

STATISTICAL CONSIDERATIONS

8.12.3.3 Differences between treatment groups were tested using repeated measures ANOVA, including factors for treatment group, center, the treatment group-by-center interaction, time and the time-by-treatment group interactions. The repeated measures ANOVA was conducted on four datasets:

1. Unbalanced set
2. Balanced set (missing values replaced by predicted values calculated from the model fitted to the available data.
3. LOCF for both between and within treatment group tests.
4. Completers; missing values were interpolated to ensure complete patient profiles.

Changes in diastolic blood pressure over the course of the study were analyzed in a similar manner to the change in body weight. The proportion of patients losing greater than 5% of baseline body weight at endpoint and over 12 weeks was compared between treatment groups using logistic regression with factors for treatment, center and the treatment group-by-center interaction. The study was powered to detect a 2.7 kg difference in bodyweight between the two groups. Differences in the proportion of patients reporting adverse events in each treatment group was analyzed using the Chi-square test. An intent-to-treat analysis was also performed for subjects who took at least one dose of study medication and had at least one post-baseline assessment.

RESULTS

POPULATIONS ENROLLED/ANALYZED

8.12.4.1 Overall, 131 patients were screened for the study; four subjects withdrew during the washout period and 127 patients were randomized to treatment. Of these patients, 14 were given study medication in error (all from center 2), by the investigator during the washout period. These subjects were withdrawn from the study. Thus, 113 patients entered the double-blind phase of the study. During the double-blind phase, 7 subjects withdrew and thus 106 patients

completed the study. A total of 127 patients received at least one dose of study medication and were included in the intent-to-treat analyses of the principal efficacy measures. Of these, 14 patients who were recruited at center 2 failed to undergo a washout and were therefore excluded from the modified intent-to-treat analyses.

Table 8.12.4.1.1 provides the baseline demographic characteristics for all patients (excluding center 2).

TABLE 8.12.4.1.1		
Demographic variable	**Sibutramine n=54**	**Placebo n=59**
Age (yrs)	47.7	48.1
Male	18	20
Female	36	39
Caucasian	53	57
Weight (kg)+	93.6	97.0
BMI (kg/m^2)	33.5	33.8

+ median values

The treatment groups were comparable for age, sex, and race. The placebo group had a higher median body weight at baseline; however, the BMIs were similar. Baseline blood pressure values were similar for the two groups.

All patients were hypertensive as required by the protocol; however, only 33% were taking anti-hypertensive drug therapy. Table 8.12.4.1.2 illustrates the anti-hypertensive medications taken by the patients in the two groups.

TABLE 8.12.4.1.2		
Anti-hypertensive agent	**Placebo**	**Sibutramine**
ACE inhibitor	9	6
β-blockers	7	6
Calcium channel blocker	7	4
Diuretics	9	8

EFFICACY ENDPOINT OUTCOMES

Body weight

8.12.4.2 The results of the analyses on the four datasets were, in general, similar. There was a statistically significant treatment group effect for the repeated measures ANOVA, as well as significant week and treatment group-by-week effects were also detected.

Figure 8.12.4.2.1

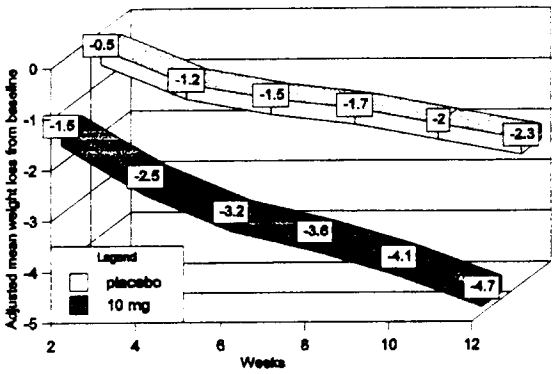
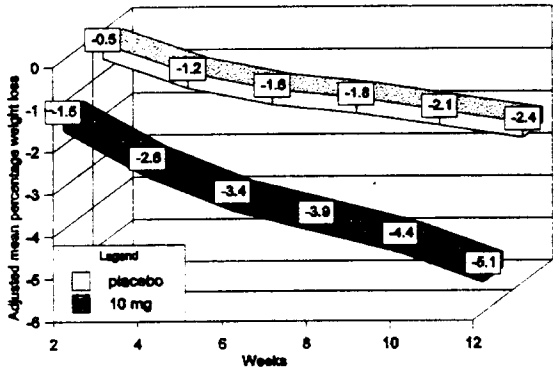


Figure 8.12.4.2.1 shows the adjusted (for center and treatment group-by-center interaction) mean change in body weight (kg) for the completers. The sibutramine group lost significantly more weight than the placebo group at weeks 2-8 ($p<0.001$) and weeks 10 and 12 ($p<0.01$).

Figure 8.12.4.2.2 illustrates the adjusted (for center and treatment-by-center interaction) mean percentage change from baseline in body weight for the completers.

Figure 8.12.4.2.2



At every time point the sibutramine group lost a significantly greater percentage of bodyweight compared to placebo ($p<0.001$).

The proportion of subjects losing greater than 5% of baseline body weight in the sibutramine group was significantly higher than the proportion in the placebo group (44 vs 17% respectively, $p=0.002$).

Waist circumference

Waist circumference was reduced by 4.0 cm in the sibutramine group and by 1.8 cm in the placebo group.

Compliance and appetite

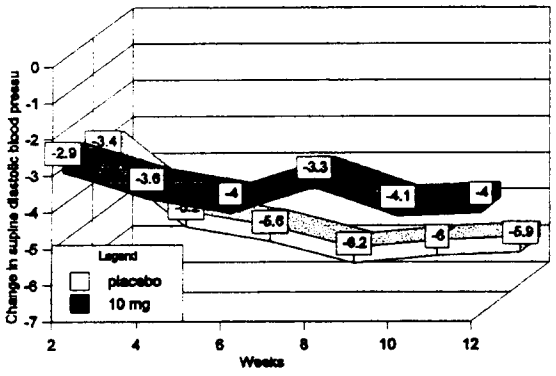
There were no statistically significant differences between the treatment groups in dietary compliance or in the hunger, appetite, satiety, snacking and craving visual analogue scales.

Blood pressure and pulse

For both treatment groups, diastolic and systolic blood pressures (supine and standing) were reduced; the differences between the groups, however, were not statistically significant.

Figure 8.12.4.2.3 provides the change from baseline in supine diastolic blood pressure for the completers.

Figure 8.12.4.2.3



It is interesting to note that although the sibutramine group lost significantly more weight during the study than the placebo group, the reductions in blood pressure were smaller in the sibutramine group compared to the reductions in the placebo group.

The change from baseline in supine pulse rate was -4.3 bpm in the placebo group and 2.4 bpm in the sibutramine group ($p<0.001$). The change from baseline in standing pulse rate was -5.8 bpm in the placebo group and -0.6 bpm in the sibutramine group ($p<0.01$).

SAFETY OUTCOMES

Adverse events

8.12.4.3 There were no statistically significant differences between the groups with respect to the incidence of reported adverse events. The most common events in the COSTART categories

were Body as a Whole, Digestive, and Nervous System. The most common events (reported by > 5% of patients) were constipation (4 placebo and 6 sibutramine), dry mouth (2 placebo and 8 sibutramine), and nervousness (5 placebo and 1 sibutramine). Two subjects in the placebo group were withdrawn from the study: one because of distention of the abdomen and one because of fever. Two sibutramine subjects were also withdrawn from the study: one because of obsessive behavior and one because of nausea and constipation. There were no reported adverse events during the 1-month follow-up period.

Clinical chemistries

The platelet count increased from baseline in the sibutramine group (14.24 × 10^9/l) and decreased in the placebo group (-0.46 × 10^9/l) ($p<0.01$). The creatine concentration was reduced in the sibutramine group (-4.40 umol/l) and decreased in the placebo group (-0.86 umol/l) ($p=0.03$). These changes were not clinically significant.

Lipoprotein lipids

The total cholesterol level decreased by 0.40 mmol/l in the sibutramine group and decreased by 0.21 mmol/l in the placebo group ($p=0.04$).

Electrocardiograms

The results of the analysis of change in heart rate from the ECG were similar to the changes observed with the manually-measured pulse rates. The QT interval was reduced in the sibutramine group (-9.3 ms) and the placebo group (-2.4 ms), ($p=0.02$); these changes were not clinically meaningful.

8.12.5 CONCLUSIONS

In this study of obese hypertensive patients, 10 mg QD of sibutramine led to a statistically significantly greater degree of weight loss than did placebo (-4.7 vs -2.3 kg, $p<0.01$). However, despite a greater reduction in body weight in the sibutramine group, the placebo group had a greater reduction in diastolic blood pressure (supine and standing). In contrast to the effect of sibutramine on blood pressure, total cholesterol levels were favorably affected by drug treatment. There were no clinically significant changes in serum chemistries noted during the study (the LFTs are not reported).

8.13. SB 3069

OBJECTIVE/RATIONALE

8.13.1 The primary objective of this open-label extension study of core trial SB2057 was to assess the long-term (6 months) efficacy, safety and tolerability of sibutramine in mild to

moderately obese, hypertensive subjects.

DESIGN

8.13.2 This study was a 12-week multicenter, open-label extension trial following the 12- week core study SB 2057, in which hypertensive patients received placebo or 10 mg QD of sibutramine. All patients regardless of receiving active drug or placebo in the core study received 10 mg QD of sibutramine during this trial.

PROTOCOL

POPULATION

8.13.3.1 Only those patients who completed SB 2057 were eligible for SB 3069. The inclusion criteria included:

1. Age _____
2. Male of female.
3. Subjects were allowed to take up to two anti-hypertensive agents.

Exclusion criteria included:

1. Diastolic blood pressure of greater than 125 mmHg.
2. Patients who had experienced a serious adverse event in study SB 2057.
3. Patients who violated the protocol of study SB 2057.

ENDPOINTS

8.13.3.2 The primary endpoints were the change in body weight and diastolic blood pressure. The major assessments were conducted at weeks 16, 20, 24, and 28. Blood pressure was recorded as the mean of three measurements.

STATISTICAL CONSIDERATIONS

8.13.3.3 The principle measure of efficacy was the change in body weight calculated on a last observation carried forward basis. The change from week 0 to week 24 for the group randomized to sibutramine in SB 2057 and the corresponding changes from week 12 to week 24 within each of the treatment groups from SB 2057 were reported with 95% confidence intervals. Changes in diastolic blood pressure over the course of the study were analyzed in a similar manner to body weight.

RESULTS

POPULATIONS ENROLLED/ANALYZED

8.13.4.1 Overall, 103 patients (113 entered SB 2057) entered into the trial between 10/93 and 5/94. Of these, 100 patients completed the study to week 24. Table 8.13.4.1.1 illustrates the baseline demographic characteristics.

TABLE 8.13.4.1.1		
Variable	**Previous treatment**	
	Sibutramine, n=49	**Placebo, n=54**
Age (yrs)	48.3	47.6
Male	17	19
Female	32	35
Caucasian	49	53
Weight (kg)❂	88.9	91.8
BMI (kg/m^2)	31.6	32.5

❂ median values

Table 8.13.4.1.2 provides the anti-hypertensive agents taken by the subjects in each baseline group. Fifty-four percent of the subjects were taking an anti-hypertensive agent.

TABLE 8.13.4.1.2		
Anti-hypertensive therapy class	**Previous treatment group**	
	Placebo	**Sibutramine**
ACE-inhibitor	9	5
β-blocker	7	7
Calcium channel blocker	7	4
Diuretics	2	3
Thiazide	6	4
Clonidine	1	0

The two groups were well matched for use of antihypertensive therapy at baseline.

EFFICACY ENDPOINT OUTCOMES

8.13.4.2 Body weight

Table 8.13.4.2.1 illustrates the mean change in absolute body weight (kg) to endpoint - LOCF.

TABLE 8.13.4.2.1					
Previous treatment	**n**	**Change from week 12 (range)**	**95% CI**	**Change from week 0 (range)**	**95% CI**
Placebo	54	-3.4	-4.2, -2.7	-5.8	-4.5, -7.1
Sibutramine	49	-1.2	-2.0, -0.5	-5.7	-7.2, -4.2

Of the 49 patients who previously received sibutramine, 16 gained weight (0.1-3.2 kg) but the majority lost weight; with 13 patients losing more than 3 kg of their week 12 body weight. Similar results were reported in the completers dataset.

Table 8.13.4.2.2 provides the mean percent change in body weight (kg) at endpoint - LOCF.

TABLE 8.13.4.2.2					
Previous treatment	**n**	**Change from week 12 (range)**	**95% CI**	**Change from week 0 (range)**	**95% CI**
Placebo	54	-3.7	-4.5, -3.0	-6.0	-7.3, -4.7
Sibutramine	49	-1.4	-2.3, -0.6	-6.1	-7.6, -4.5

The results were essentially the same for the completers analysis and indicate that 24 weeks of treatment with sibutramine led to a statistically significant reduction in body weight.

Figure 8.13.4.2.1

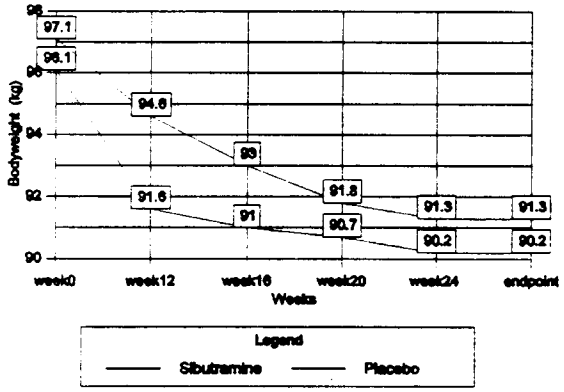


Figure 8.12.4.2.1 illustrates the absolute change in body weight for the sibutramine and placebo groups. It must be kept in mind that the placebo group received placebo from week 0 to week 12 at which time they began 10 mg QD of sibutramine.

Figure 8.13.4.2.1 illustrates that the greatest rate of weight loss (steepest slope of line) occurs during the first 12 weeks of drug treatment.

It is interesting to examine the proportion of patients who lost greater than 5% of week-0 and

week-12 body weight. These data are shown in table 8.13.4.2.3.

TABLE 8.13.4.2.3					
Target	**Change from**	**Previous tx**	**n**	**%**	**95% CI**
>5% of week0 weight	week 0 to endpoint	sibutramine	49	59	45, 73
		placebo	54	57	44, 71
>5% of week12 weight	week 12 to endpoint	sibutramine	49	8	0.5, 16
		placebo	54	28	16, 40

These data suggest that the majority of the weight loss effect of the drug is present by week 12 of treatment.

Waist circumference

In the week 0 to endpoint analysis, the sibutramine group had a 5.1 cm reduction in waist circumference and the placebo group lost 5.0 cm from their waist circumference. These were both statistically significant within group changes.

Blood Pressure

The changes in diastolic blood pressure (DBP) in the completers dataset are shown in table 8.13.4.2.4.

TABLE 8.13.4.2.4		
Variable	**Mean change (95% CI) by previous treatment**	
	Placebo n=53	**Sibutramine n=47**
Week 12 to week 24		
Supine DBP (mmHg)	-0.9	-2.5
Standing DBP (mmHg)	-0.2	-3.6
Week 0 to week 24		
Supine DBP (mmHg)	-7.4	-6.1
Standing DBP (mmHg)	-6.7	-7.1

In the completers dataset, from week 0 to week 24, the reductions in diastolic blood pressure were similar for the placebo and sibutramine groups. The results for systolic blood pressure were similar.

It is interesting to note that, whereas there were statistically significant correlations between the reduction in body weight and the reduction in systolic and diastolic blood pressures in the sibutramine-treated subjects in the core study SB2057, these correlations were no longer significant when analyzed at endpoint in the extension study SB3069. The correlation coefficients for the change in body weight vs the change in blood pressure are depicted below in table 8.1.4.2.5.

TABLE 8.13.4.2.5 Correlation between the Δ in body weight vs the Δ in blood pressure at endpoint				
Blood pressure		**Core study SB2057**		**Extension study SB3069**
		Sibutramine	Placebo	Sibutramine●
Supine	DBP	0.36 p=0.007	0.39 p=0.002	0.19 p=0.2
	SBP	0.28 p=0.04	0.34 p=0.008	0.15 p=0.3
Standing	DBP	0.37 p=0.006	0.39 p=0.002	0.14 p=0.3
	SBP	0.27 p=0.05	0.32 p=0.01	0.20 p=0.2

● individuals randomized to sibutramine in the core study SB2057 and continued into SB3069

Pulse rate

The changes in pulse rate during the study are shown in table 8.13.4.2.6

TABLE 8.13.4.2.6		
Variable	**Mean change (95% CI) by previous treatment**	
	Placebo n=53	**Sibutramine n=47**
Week 12 to week 24		
Supine pulse rate (bpm)	6.7	2.1
Standing pulse rate (bpm)	5.5	1.6
Week 0 to week 24		
Supine pulse rate (bpm)	2.0	4.3
Standing pulse rate (bpm)	-0.3	0.3

The results of the completers dataset analyses were similar to the above endpoint analyses and indicate that sibutramine treatment increases pulse rate.

SAFETY OUTCOMES

8.13.4.3 Adverse Events

As expected, the number of patients who reported an adverse event was greater in the sibutramine group from week 0 to week 24 (61%) compared to the sibutramine group from week 12 to week 24 (37%). Thirty-seven patients who received placebo during the core study and sibutramine from week 12 to week 24 reported an adverse event. The most common body systems by COSTART included Body as a Whole, Cardiovascular, and Nervous Systems. The individual complaints by group and week of drug ingestion are not compared statistically. Dry mouth and back pain were reported by more than 5% of patients (six patients in each case).

Seven potentially serious adverse events were reported; all of these patients completed the trial. Details of these events are shown in table 8.13.4.3.1

TABLE 8.13.4.3.1

Number	Gender	Age	Duration	Event	Comment
3	F	64	84	LBBB on ECG	possible silent MI?
22	M	47	148	A Fib dx from ECG	RBBB also present, LAHB on screening ECG
29	M	51	84	Repolarization abnormality on ECG	Outcome of event unknown
60	F	54	148	Sciatica	had surgery and recovered
65	M	38	5	Lumbago	corrective surgery was performed
93	M	63	44	Pernicious anemia	treated with Vitamin B_{12}
116	M	61	79	Syncope	medical hx of cerebral infarction, aortic aneurism, tension headaches

Three patients were withdrawn from the study because of an adverse event. The details of these withdrawals are provided in table 8.13.4.3.2

TABLE 8.13.4.3.2

Number	Gender	Age	Duration	Event	Comment
33	F	34	1	nausea	resolved when drug stopped
38	F	37	112	insomnia	resolved when drug stopped
138	M	37	84	gastric pain	resolved when drug stopped

One serious post-study event was recorded. Patient # 138, a 37 year old male, suffered a myocardial infarction and died from ventricular fibrillation. The death occurred two weeks and one day after being withdrawn from the extension trial at week 24 because of stomach pains. He had a history of stenosis of the left anterior descending coronary artery treated with PTCA one year previously.

Clinical laboratory evaluation

The statistically significant changes in laboratory assessments after 24 weeks of treatment with sibutramine are shown in table 8.13.4.3.3

TABLE 8.13.4.3.3

Variable	Number of patients	Mean change from baseline	95% CI
Hemoglobin (mmol/L)	47	-0.13	-0.23, -0.03
Mean cell volume (fl)	43	1.74	0.35, 3.14
Platelets ($\times 10^9$/L)O	47	9.00	2.50, 14.50
Chloride (mmol/L)	47	-2.02	-2.96, -1.08
Creatine (umol/L)O	47	-3.00	-6.00, -1.00
Total protein (g/L)	46	-2.67	-3.64, -1.70
Albumin (g/L)	46	-1.09	-1.90, -0.28
AST (U/L)O	46	6.50	4.50, 9.00

O Hodges-Lehmann estimate of median change

None of the above changes were clinically significant.

Lipoprotein Lipid Levels

A summary of the changes in lipid levels is provided in table 8.13.4.3.4

TABLE 8.13.4.3.4

Lipid Level (mmol/L)	Mean change (95% CI) from baseline to endpoint by previous treatment	
	Placebo n=53	Sibutramine n=47
Total cholesterolO	-0.05	-0.20
LDL cholesterol	0.02	-0.07
HDL cholesterol	0.03	0.01

TABLE 8.13.4.3.4		
Lipid Level (mmol/L)	Mean change (95% CI) from baseline to endpoint by previous treatment	
	Placebo n=53	Sibutramine n=47
Triglycerides✪	0.00	-0.45
VLDL	-0.03	-0.17

✪ Hodges-Lehmann estimate of median change

There were statistically significant reductions in total cholesterol, triglycerides, and levels of VLDL in the group that received sibutramine for 24 weeks

Electrocardiograms.

Other than an increase in heart rate, there were no clinically significant changes in ECG parameters.

8.13.5 SPONSOR'S CONCLUSIONS

"The changes observed in this study support the conclusion of the core study. Continued therapy with sibutramine 10 mg induced further weight loss without increasing blood pressure and therefore did not adversely affect the management of hypertension in this patient population. Overall, the small increase in pulse rate was not considered to be clinically significant and sibutramine was well tolerated."

8.13.6 MEDICAL OFFICER'S CONCLUSIONS

The mean absolute weight loss (kg) from week 0 to week 24 in the sibutramine group was statistically significant: 5.7 kg; the 95% CI was -7.2, -4.2 kg with a range of
These findings indicate that 10 mg QD of sibutramine may produce significant weight loss in a subset of hypertensive patients with the maximum effects occurring during the first 12 weeks of therapy. In terms of blood pressure control, the group treated with sibutramine for 24 weeks had a 6.5 mmHg reduction in diastolic blood pressure. The direct correlation between sibutramine-induced weight loss and the reduction in blood pressure was evident at completion of the 12-week core study SB2057, but was absent in the extension study. These data underscore sibutramine's inability to consistently reduce both body weight and blood pressure. The increase in pulse rate of approximately 4 bpm may have been attenuated by the concomitant use of calcium channel and β-blockers.

In general, the adverse events reported were not serious and were consistent with those reported in the other trials. However, in this group of higher-risk individuals, by nature of their hypertension, four serious cardiovascular events were reported: three during the trial and one following the trial. These events were: 1) new LBBB; 2) atrial fibrillation; 3) a new

repolarization abnormality on ECG; and 4) a death from an acute myocardial infarction in a 37 year old male with a history of coronary artery disease. The patient suffered the infarction 15 days post-study. The enhanced sympathetic tone induced by sibutramine may represent a potential risk in obese individuals with cardiac disease.

COMPARATIVE STUDIES

8.14 SB 2053

OBJECTIVE/RATIONALE

8.14.1 The principle objective of this study was to compare the efficacy and tolerability of 10 mg QD of sibutramine to 15 mg BID of dexfenfluramine in obese subjects.

DESIGN

8.14.2 This study was a 12-week, multicenter, randomized, double-blind, parallel-group comparison of sibutramine with dexfenfluramine in 237 obese patients. There was a 1 to 2 week wash-out period followed by a 12-week double-blind treatment phase. There was also a 4-week follow-up phase following active treatment.

PROTOCOL

POPULATION

8.14.3.1 Entry criteria for this study included patients aged _____years, male or female, and obese with a BMI $\geq$ 27 kg/m^2. Relevant exclusion criteria included patients with IDDM or insulin-requiring NIDDM, patients taking anorectic agents or antidepressants, antiserotoninergics, barbiturates, and neuroleptics.

ENDPOINTS

8.14.3.2 The endpoints included changes in body weight, waist and hip circumferences, vital signs, serum chemistries, measures of appetite, and documentation of any adverse events.

STATISTICAL CONSIDERATIONS

8.14.3.3 In the analyses of actual weight loss, the equivalence parameter was 2 kg (i.e. the treatments will be considered equivalent if the difference between the two groups in less than 2 kg). For percentage weight loss, the equivalence range was the arithmetic difference of 2.5%. Differences between treatment groups in the change from baseline in body weight was analyzed using repeated measures ANOVA including factors for treatment group, time, and the treatment group-by-time interaction.There were 4 datasets:

1. Unbalanced analysis-all available data with no account taken of missing values.
2. Balanced analysis-all available data with the addition that for the within group tests, the missing values are replaced by predicted values calculated from the model fitted to the data.
3. LOCF.
4. Completers-patients who complete the 12 week treatment phase.

For the secondary measures of efficacy, the results were presented as 95% confidence intervals for the difference between the two treatment groups. The overall percentages of patients reporting adverse events in each treatment group were compared using the 90% confidence interval based on the Chi-square test. The 95% confidence intervals for the difference based on two sample t-tests were used to assess the change to endpoint and week 12 for blood pressure and pulse.

RESULTS

POPULATIONS ENROLLED/ANALYZED

8.14.4.1 Two-hundred thirty-seven patients were screened into the study at 38 centers. Eleven patients withdrew before the baseline visit; 226 patients were entered into the double-blind phase. One-hundred twelve subjects were randomized to sibutramine and 114 were randomized to dexfenfluramine. One-hundred two subjects completed the study in the sibutramine group and 95 completed in the dexfenfluramine group. There was a statistically significantly lower risk of withdrawal in the sibutramine group compared to the dexfenfluramine group (90% CI 0.28, 0.95). Table 8.14.4.1.1 provides the baseline characteristics for the two groups.

TABLE 8.14.4.1.1

	Sibutramine n=112	**Dexfenfluramine n=114**
Age (yrs)	38.9	38.8
Gender	101 female	106 female
Race	111 Caucasian	111 Caucasian
Weight (kg)	84	86
BMI* (kg/m^2)	33.3	33.7

Values in parentheses are ranges
* represent median values
* baseline BMI was 40.2 kg/m^2 for the sibutramine males and 34.2 kg/m^2 for the males in the dexfenfluramine group.

There were 9 subjects in the dexfenfluramine group and 4 subjects in the sibutramine group taking antihypertensive agents at baseline. Six of the dexfenfluramine and 2 of the sibutramine subjects were taking diuretics and antidiuretics. Fourteen sibutramine and 7 dexfenfluramine subjects were taking estrogens at baseline. Five dexfenfluramine and 1 sibutramine subject were

taking hypoglycemic agents. During the study, 11 sibutramine and 2 dexfenfluramine subjects started laxatives.

The withdrawal rates and reasons for withdrawal are summarized in table 8.13.4.1.2

TABLE 8.13.4.1.2		
Reason for withdrawal	Sibutramine n=112	Dexfenfluramine n=114
Adverse events	6	11
Lack of efficacy+	2	3
Withdrew consent	2	4
Unable to attend	0	1

+The two patients in the sibutramine group that withdrew because of lack of efficacy lost -5.4 and -2.0 kg of weight at 74 and 39 days, respectively. The 3 subjects who withdrew in the dexfenfluramine group gained 1.5, 3.5, and 1.0 kg of weight at 47, 45, and 47 days, respectively.

EFFICACY ENDPOINT OUTCOMES

Body weight

8.13.4.2 Table 8.13.4.2.1 illustrates the actual change in body weight (kg) by treatment group for intent-to-treat patients included in the balanced dataset.

TABLE 8.13.4.2.1					
Variable	**Week**	**Treatment group**			
		Sibutramine		**Dexfenfluramine**	
Weight (kg)		N	Mean	N	Mean
	Baseline	112	89.1	112	88.5
	4	112	-2.8	112	-2.0
	8	112	-4.0	112	-2.9
	12	112	-4.6	112	-3.4
	overall change	112	-3.8	112	-2.8
90% CI for difference -1.6,-0.4◇					

◇Equivalence interval is -2kg, +2kg

The results of all the analyses comparing the amount of weight lost in the two groups were very similar. In general, it could not be concluded that one drug was more efficacious than the other.

The results of the percentage change in body weight were similar to the analysis of the change in absolute body weight: the sibutramine group lost approximately 4.3% of baseline body weight and the dexfenfluramine group lost approximately 3.2 %. These differences were not statistically significant.

In the completers dataset, 48% of the sibutramine subjects lost >5% of baseline body weight and 38% of the dexfenfluramine subjects met this goal.

Waist circumference

Waist circumference decreased by 4.3 cm in the sibutramine group and by 4.0 cm in the dexfenfluramine group.

Consummatory behavior

There were no statistically significant differences between the groups for the visual analogue scales. The reduction in the number of calories consumed and reductions in calories from carbohydrates, protein, fat, and alcohol were similar for the two groups.

SAFETY OUTCOMES

Adverse events

8.13.3 Table 8.6.4.3.1 provides the number of patients in each group reporting the most common (reported by 5% of subjects) adverse event by COSTART system.

TABLE 8.13.3.1

COSTART term	Sibutramine n=112	Dexfenfluramine n=114
Asthenia	7	16
Flu syndrome	18	11
Headache	15	13
Infection	3	10
Abdominal pain	6	8
Constipation	18	4
Diarrhea	1	12
Nausea	6	7
Dry mouth	15	11

TABLE 8.13.3.1		
COSTART term	**Sibutramine n=112**	**Dexfenfluramine n=114**
Insomnia	6	9
Pharyngitis	6	6

Fourteen patients were withdrawn from the study due to an adverse event. Details of these events are provided in Table 8.13.3.2

TABLE 8.13.3.2						
Number	**Sex**	**Age**	**Drug**	**Duration**	**Event**	**Comment**
31	F	51	Sib	28	severe migraine	resolved with acetylsalicylate
34	F	48	Sib	77	severe nausea and headache	remained six weeks post-withdrawal
72	F	28	Sib	63	moderate depression	recovered 1-week after withdrawal
147	F	35	Sib	56	headaches	resolved 1-day after withdrawal
199	F	48	Sib	6	urticaria	resolved 2-weeks after withdrawal
231	F	27	Sib	49	abdominal pain flushing	resolved 1-week after withdrawal
13	F	38	Dex	33	severe headaches	resolved 2-days after withdrawal
27	F	27	Dex	26	headaches, epigastric pain	resolved 1-day after withdrawal
37	F	33	Dex	28	palpitations, orthostatic hypotension	resolved 1-month after withdrawal
62	F	29	Dex	35	asthenia, diarrhea	?
75	F	24	Dex	16	nausea, vomiting	?
94	F	40	Dex	6	headache, nausea, vomiting	resolved 2-days after withdrawal
139	F	22	Dex	22	facial erythema	resolved 5-days after withdrawal
186	F	33	Dex	7	dizziness	resolved 1-day after withdrawal

Clinical chemistries

There were no clinically significant changes in the serum chemistry values for either group.

Lipoprotein lipids

Total cholesterol decreased by -4.43% and -6.33% in the sibutramine and dexfenfluramine groups, respectively. The mean percent change from baseline in triglyceride levels were -13.99% and -8.55% for the sibutramine and dexfenfluramine groups, respectively. These differences were not statistically significant.

Vital signs

There were statistically significant differences in the changes in diastolic blood pressure and pulse rate between the two groups. Diastolic blood pressure increased by 1.9 mmHg in the sibutramine group and decreased by 1.5 mmHg in the dexfenfluramine group. The pulse rate increased in the sibutramine group 3.6 bpm and decreased by 0.9 bpm in the dexfenfluramine group.

Electrocardiograms

There were no significant changes in the ECG parameters in either group.

Post-treatment follow-up

Spontaneous reporting during the 4-week follow-up period did not reveal any evidence of withdrawal phenomena for either drug.

8.13.5 SPONSOR'S CONCLUSIONS

"Weight loss occurred with both treatments and this study demonstrated that sibutramine 10 mg given once-daily and dexfenfluramine 15 mg twice-daily were equivalent in terms of both actual and percentage weight loss in obese patients. Both drugs had similar safety profiles with the exception of statistically significant increases in mean pulse rate and standing diastolic blood pressure with sibutramine compared to dexfenfluramine."

8.13.6 MEDICAL OFFICER'S CONCLUSIONS

This Reviewer agrees with the Sponsor's conclusions.

In this 12-week study of obese, primarily Caucasian women, 10 mg QD of sibutramine produced an equivalent amount of weight loss as 15 mg BID of dexfenfluramine. Despite similar degrees of weight loss, sibutramine produced elevations in mean pulse rate and standing diastolic blood

pressure. The reported adverse events were consistent with the known pharmacological effects of the two drugs.

8.14 SB 1052

OBJECTIVE/RATIONALE

8.14.1 The objective of this 12-week study was to compare the efficacy and the tolerability of 10 mg QD of sibutramine with 30 mg QD of dexfenfluramine and placebo in moderately obese subjects.

DESIGN

8.14.2 This was a 12-week multicenter, double-blind, randomized, placebo-controlled, parallel-group study of 75 obese subjects: 25 subjects in each treatment arm. There was a 1- week washout phase during which time the subjects received general written and verbal dietary instructions. The 12-week active-treatment phase was followed by a 4-week follow-up visit. Because of reports of depression associated with abrupt withdrawal of dexfenfluramine, a protocol amendment dated September 4, 1992 stated that during week 11 the dexfenfluramine subjects take only 15 mg QD of the drug.

PROTOCOL

POPULATION

8.14.3.1 Entry criteria for the study included obesity:BMI kg/m^2, male and female subjects aged years and in a good state of health. Subjects controlled on a hypertensive agent(s) during the preceding 6 months were allowed to participate in the study.

ENDPOINTS

8.14.3.2 The primary endpoint was the change in body weight from baseline; weight was measured at screening, and baseline, and every week during the 12-week active phase, as well as at week 16. Waist and hip circumferences were measured at baseline and again at week 12. The CGI depression scale, alcohol usage, tobacco usage, laboratory assessments, patient self-assessments of hunger and appetite, and vital signs were examined at regular intervals during the study.

STATISTICAL CONSIDERATIONS

8.14.3.3 As with previous studies, the original protocol does not detail the statistical procedures. The study was planned to detect a difference between treatment groups in mean change in body weight to endpoint of 3.8 kg. For the primary efficacy parameter, change in weight from

baseline, repeated measures ANOVA was performed with several interaction terms. Fisher's protected LSD method was used to compare differences between groups when an overall effect was confirmed. The repeated measures ANOVA was performed on 4 datasets:
1). Unbalanced analysis
2). Balanced analysis
3). LOCF
4). Completers

Heterogeneity of variances was documented for the weight loss data and therefore compensation was made when conducting multiple comparisons. In addition, an imbalance was found in baseline body weight between the groups. The correlation between the change in weight from baseline to endpoint and the average of the baseline and endpoint values was examined and found to be -0.08, p=0.56. Thus, a simple change model was therefore considered to be appropriate. The Mantel-Haenszel Test was used to compare the proportion of patients with a reduction of greater than 5% of baseline weight at endpoint and at week 12.

RESULTS

POPULATIONS ENROLLED/ANALYZED

8.14.4.1 Overall, 77 patients were screened for entry into the study. Two patients withdrew during the washout phase, thus, 75 patients entered the double-blind phase: 24 to placebo, 25 to dexfenfluramine, and 26 to sibutramine. A total of 52 patients completed the 12 week study: 17/24 placebo, 16/25 dexfenfluramine, 19/26 sibutramine. Table 8.14.4.1.1 illustrates the reason for withdrawal from the study by treatment group.

TABLE 8.14.4.1.1

Reason for withdrawal	Placebo	Dexfenfluramine	Sibutramine
	n=24	n=25	n=26
Adverse event	2	2	0
Lack of efficacy	1	0	0
Lost to follow-up	3	5	4
Protocol violation•	0	2	1
Withdrew consent	1	0	2
Total withdrawn	7 (29%)	9 (36%)	7 (27%)

There were no statistically significant differences between the groups for withdrawal rates
• did not attend follow-up visits

There were a number of protocol violations, compliance violations and discrepancies in timing

of assessments in all groups. They appeared to be balanced among treatment groups and it is unlikely that they affected the study results.

Two patients (placebo group) did not provide a post-baseline assessment of body weight and were not included in any of the efficacy analyses. Sixty-nine patients provided an assessment of body weight after week 2 and were included in the primary measures efficacy analyses. Four patients were withdrawn during the follow-up period, but provided an assessment of body weight at week 12.

Table 8.14.4.1.2 provides the baseline demographic variables for the 3 groups.

TABLE 8.14.4.1.2

Variable	Placebo	Dexfenfluramine	Sibutramine
	n=24	n=25	n=26
Age (yrs)	41.4	42.1	41.9
Sex (% female)	88%	80%	73%
Race (% Caucasian)	100%	100%	100%
Weight (kg)✚	84.5	87.6	87.4
BMI (kg/m^2)	32.5	33.7	33.6

✚ median values

The men in the dexfenfluramine group had a higher baseline BMI: 35.3 kg/m^2; compared to placebo subjects: 31.3 kg/m^2; and sibutramine-treated individuals: 34.6 kg/m^2.

EFFICACY ENDPOINT OUTCOMES

Body weight

8.14.4.2 It should be noted that for the completers dataset there was no statistically significant week-by-treatment group interaction. The results of the unbalanced dataset analysis for actual weight loss at each time point during the study for the 3 groups are shown in Table 8.14.4.2.1

TABLE 8.14.4.2.1

Week	Group	n	Adjusted mean change (kg)
2	Pl	21	-0.7
	Dex	23	-1.8**
	Sib	24	-2.0**

TABLE 8.14.4.2.1			
Week	**Group**	**n**	**Adjusted mean change (kg)**
4	Pl	22	-1.1
	Dex	23	-3.0**
	Sib	24	-2.8**
6	Pl	20	-1.0
	Dex	20	-4.0***
	Sib	20	-3.7***
8	Pl	18	-1.4
	Dex	22	-3.8**
	Sib	22	-4.0**
10	Pl	17	-2.1
	Dex	19	-3.7
	Sib	21	-4.8**
12	Pl	15	-2.9
	Dex	18	-4.1
	Sib	20	-5.2

** $0.05 \leq p < 0.01$ *** $0.001 \leq p < 0.01$ compared to placebo
Pl=placebo, Dex=dexfenfluramine, Sib=sibutramine

The results of the analysis on the balanced dataset was similar to the unbalanced dataset analysis.

Figure 8.14.4.2.1

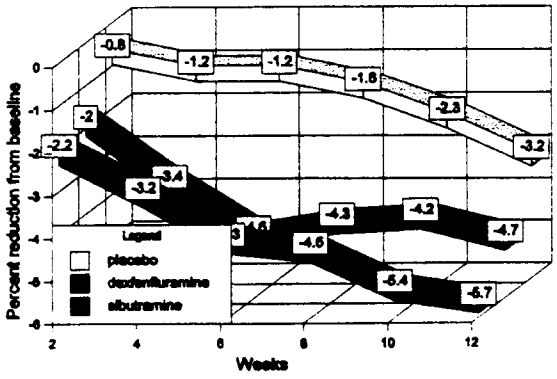


Figure 8.14.4.2.1 illustrates the adjusted mean change in percentage weight loss from baseline.

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There were no statistically significant differences in weight loss between patients who received sibutramine and those who received dexfenfluramine. The sibutramine group had a statistically significantly greater percentage weight loss than placebo patients at all weeks except week 12. The adjusted mean percentage weight loss at endpoint was 4.8% for the sibutramine group, 4.5% for the patients who received dexfenfluramine, and 2.4% for placebo patients; these differences were not statistically significant.

There were no statistically significant differences among the three groups with respect to the proportion of patients losing greater than 5% of baseline body weight (completers dataset at week 12: 40%, 41%, and 55% for the placebo, dexfenfluramine, and sibutramine groups, respectively).

Waist circumference

In an endpoint analysis, the reduction in waist circumferences were 4.0, 4.6, and 2.5 cm in the sibutramine, dexfenfluramine, and placebo groups, respectively.

Consummatory behavior

There were no statistically significant differences among the treatment groups for the changes to endpoint in the hunger, appetite, and eating visual analogue scales. There were no differences among the groups with respect to changes in dietary compliance.

SAFETY OUTCOMES

Adverse events

8.14.4.3 There were no statistically significant differences in the proportions of patients in each group reporting an adverse event. However, the dexfenfluramine group reported significantly more adverse events in the digestive system (diarrhea) compared to the sibutramine or placebo groups. Reports in Body as a Whole (infections) and Nervous System (dry mouth) were significantly greater in the dexfenfluramine and sibutramine groups than in the placebo group. There did not appear to be any significant differences among the groups in the percentage of patients reporting severe adverse events.

Table 8.14.4.3.1 provides the details of the patients who withdrew from the study.

TABLE 8.14.4.3.1

Number	Sex	Age	Drug	Duration	Event	Comment
59	F	44	Pl	77	stroke	recovered
16119	M	43	Dex	42	renal calculus	recovered

TABLE 8.14.4.3.1						
Number	**Sex**	**Age**	**Drug**	**Duration**	**Event**	**Comment**
57	F	58	Pl	42	blackout, amnesia	recovered
30	F	20	Dex	77	hot flashes, dizziness	recovered
38—	F	24	Sib	36	daughter ingested 8 capsules	recovered without event

Serum chemistries

The only statistically significant change in a serum chemistry value was a mean increase of 14.1 U/l in creatinine kinase in the sibutramine group and a mean decrease of 20.4 U/l in the dexfenfluramine group. These changes were not clinically significant.

Lipoprotein lipids

There were no statistically significant differences in the changes in lipid levels among the groups.

Vital signs and electrocardiograms

There were no statistically significant differences among the three groups with respect to blood pressure, heart rate, or ECG parameters.

Clinical Global Impression

There were no significant group changes in depressive symptoms as measured by the Clinical Global Impression scale at week 12. The week 16 values are not reported.

8.10.5 SPONSOR'S CONCLUSIONS

"This study clearly demonstrated significantly greater weight loss during treatment with sibutramine and dexfenfluramine compared to placebo with no statistically significant differences between the two active treatments. Safety and tolerability of the two treatments were acceptable."

8.10.6 MEDICAL OFFICER'S CONCLUSIONS

This Reviewer concurs with the Sponsor's conclusions.

This 12-week study comparing the efficacy of 10 mg QD of sibutramine with 30 mg QD of dexfenfluramine and placebo reported that the active-drug treatments were comparable and both produced significantly more weight loss than placebo. There were no significant changes in serum chemistry values or vital signs during the study. There were no significant adverse events reported with the use of sibutramine, and in general, the drug was well tolerated.

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9. OVERVIEW OF EFFICACY

Table 9.1 Results of the pivotal studies conducted in patients with uncomplicated obesity.

TABLE 9.1								
Study	Dose	Duration	% completed	Δ % Wt	5% responders	ΔSBP	ΔDBP	ΔPulse
PIVOTAL - UNCOMPLICATED OBESITY STUDIES								
852	Pl	6 months	55	-1.3	20%	1.7	0.8	0.6
	1mg		65	-2.8	25%	1.2	0.3	0.3
	5mg		70	-3.7	37%	2.5	2.1	3.3
	10mg		63	-5.8	60%	4.2	2.8	6.0
	15mg		60	-7.4	67%	3.4	2.7	6.1
	20mg		58	-8.6	72%	5.0	4.0	7.0
	30mg		55	-9.4	77%	4.1	3.3	5.3
1047	Pl	12 months	50	-1.9	29%	-0.9	0.1	-0.2
	10mg		51	-5.5	56%	-0.3	-0.2	0.4
	15mg		59	-7.2	65%	2.7	2.0	1.5
852X• open label study	15mg	12 months	56	Na	Na	6.2	1.8	4.7
	20mg			Na	Na	6.6	3.1	8.4
	25mg			Na	Na	6.8	2.2	8.0
	30mg			Na	Na	6.1	1.3	7.8
	15mg	18 months	38	Na	Na	5.9	5.3	8.4
	20mg			Na	Na	10.8	8.4	7.8
	25mg			Na	Na	7.2	2.7	7.6
	30mg			Na	Na	7.8	3.0	6.9

SBP=systolic blood pressure and DBP=diastolic blood pressure in mm Hg; pulse in beats per minute.
• doses represent modal dose = dose most frequently taken
Na=not available

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Table 9.2 Results of short-term studies in patients with uncomplicated obesity.

TABLE 9.2								
Study	Dose	Duration	% completed	Δ % Wt	5% responder	Δ SBP	Δ DBP	Δ Pulse
NON-PIVOTAL - UNCOMPLICATED OBESITY STUDIES								
1042	Pl	12 weeks	47	-4.0	42%	-7.4	-2.8	-1.5
	1mg		38	-4.3	44%	-3.0	-1.0	1.7
	10mg		48	-7.7	74%	-3.8	-0.9	0.0
	20mg		61	-9.1	83%	-7.6	-4.4	-1.1
850	Pl	8 weeks	95	-1.3	Na	5.8	0.8	-1.4
	5mg		95	-3.0	Na	5.2	3.4	2.7
	20mg		88	-5.0	Na	4.2	3.7	3.6
851	Pl	12 weeks	69	-	Na	3.2	-1.4	-7.5
	10mg		94	-	Na	-2.4	0.9	1.3
1043	Pl	12 weeks	80	-1.7	19%	-1.2	0.5	-2.0
	5mg		84	-3.1	23%	3.4	0.5	1.2
	10mg		83	-6.1	53%	0.9	2.2	3.8
	15mg		84	-5.8	58%	0.6	0.4	4.2

Na = not available

The efficacy evaluation for obesity drugs as outlined in the Guidance for the Clinical Evaluation of Weight-Control Drugs include several potential parameters: (1) The mean weight loss in the drug-treated subjects must be statistically significantly different from the mean weight loss in subjects receiving placebo; (2) the drug-treated patients must have a mean percent weight loss from baseline that is 5% greater than the mean percent loss of the placebo group; (3) alternatively, it may be shown that the proportion of subjects who reach and maintain a loss of at least 5% of initial body weight is greater in subjects on drug compared to those receiving placebo.

The data from the two pivotal studies indicate that: (1) doses of 15-30 mg QD of sibutramine are associated with a mean percent weight loss from baseline that is at least 5% greater than that achieved with placebo and is statistically significantly different; and (2) a greater percentage of patients taking 5-30 mg QD of sibutramine achieve a loss of at least 5% of initial body weight when compared to placebo subjects. Thus, the submitted data support the "efficacy" of sibutramine, as defined in the Guidance.

Table 9.3 Results from studies of obese patients with non-insulin dependent diabetes mellitus and hypertension.

TABLE 9.3											
Study	Dose	Duration	% completed	Δ % Wt	Δ SBP	Δ DBP	Δ Pulse	Δ HbA1c	Δ fasting G	Δ G area	Δ I area
—			**NON-INSULIN DEPENDENT DIABETES MELLITUS STUDIES**								
853	Pl	12 weeks	100	-1.0	5.3	1.7	-1.7	0.1 %	22 mg/dl	Na	Na
	20mg		75	-3.0	4.8	-0.6	6.2	0.1 %	9 mg/dl	Na	Na
3051	Pl	12 weeks	91	-0.3	-0.1	2.1	0.5	0.1 %	14 mg/dl	Na	Na
	15mg		91	-2.8	-0.3	3.1	7.3	-0.3 %	-5 mg/dl	Na	Na
3068x	15mg	6 months	70	-3.8	0.8	3.6	10	0.0 %	-3.6 mg/dl	-0.15	8.5
			HYPERTENSION STUDIES								
855● ◆	Pl	8 weeks	100	-	-1.8	-7.7	3.5	NA	NA	NA	NA
	20mg		90	-	8.9	3.7	15.1	NA	NA	NA	NA
2057	Pl	12 weeks	93	-2.4	-5.6	-5.4	-4.3	NA	NA	NA	NA
	10mg		95	-5.1	-5.5	-3.7	2.4	NA	NA	NA	NA
3069x	10mg	6 months	87	-6.1	-6.1	-2.5	4.3	NA	NA	NA	NA

ΔG area = the change in incremental fasting glucose levels in mol/l.min; ΔI area = the change in incremental fasting insulin levels in mmol/l.min.

● Subjects were told to maintain body weight

◆ Blood pressure and pulse data are the week 8 overall values from 24-hour ambulatory monitoring.

Na = not available; NA = not applicable

The short-term use of 15 and 20 mg QD of sibutramine in non-insulin dependent diabetic patients was associated with clinically insignificant amounts of weight loss. The use of 15 mg QD of sibutramine for 6 months (3 months placeo-controlled and 3 months open-label) resulted in a mean percent reduction in body weight of 3.8% compared to an approximate 7 to 8% reduction in weight in obese nondiabetic patients taking 15 mg QD in the pivotal studies.

Obese, hypertensive subjects who recieved 10 mg QD of sibutramine for up to 6 montsh lost a similar percentage of weight (-5.1%) as obese, normotensive subjects taking the same dose in the pivotal studies.

Thus, whereas the data support sibutramine's efficacy in obese, hypertensive patients, there is no evidence that sibutramine is an effective weight-loss agent in non-insulin dependent diabetic patients.

Table 9.4 Results of studies comparing sibutramine with dexfenfluramine.

TABLE 9.4								
Study	Dose	Duration	% completed	Δ % Wt	5% responders	Δ SBP	Δ DBP	Δ Pulse
ACTIVE CONTROL STUDIES								
2053	10mg Sibutramine	12 weeks	91	-4.3	48%	0.7	2.3	3.4
	30mg Dex		83	-3.2	38%	0.7	-2.0	-1.3
1052	10mg Sibutramine	12 weeks	73	-5.7	55%	1.0	1.2	1.9
	30mg Dex		64	-4.7	41%	-0.7	-1.7	-4.2
	Pl		71	-3.2	40%	-4.9	-5.1	-3.6

The data from the two comparative studies indicate that 10 mg QD of sibutramine and 30 mg QD of dexfenfluramine are equivalent in terms of weight loss efficacy.

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10. OVERVIEW OF SAFETY

10.1.1 Exposure and Demographics

Table 10.1.1 illustrates the number of unique subjects exposed to sibutramine as of September 30, 1994.

TABLE 10.1.1			
Study population	**US studies**	**European studies**	**Total**
All obese patients	1051	991	2042
Depressed patients	831	194	1025
Volunteers	170	260	430
All subjects	2052	1445	3497

Exposure denominators

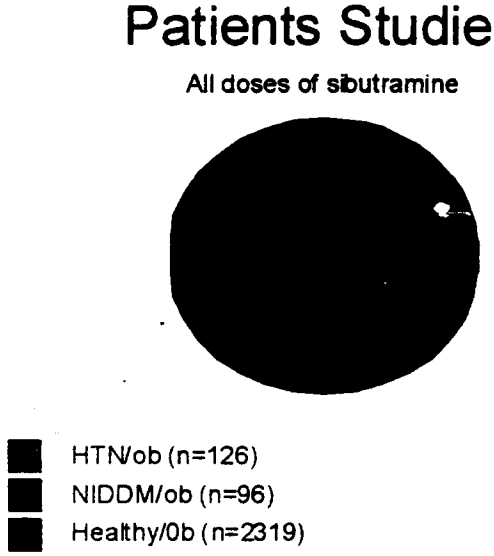
A patient who received sibutramine in either of the European placebo-controlled studies SB 2057 and SB 3051, who also received sibutramine in the open extension studies SB 3069 and SB 3068, respectively, was counted once, since there was little or no interruption of therapy between studies. In addition, a patient who received sibutramine in either of the US placebo-controlled studies BPI 852 or BPI 806, who also received sibutramine in the open extension study BPI 852X or BPI 806X, was counted twice (as two sibutramine exposures), due to an interruption in therapy between the studies (at least 6 weeks for BPI 852; and approximately 10 days for BPI 806). This Reviewer does not believe that these subjects should be counted as two unique exposures.

Table 10.1.2 provides the number of subjects exposed to sibutramine as of September 30, 1994 by mean daily dose.

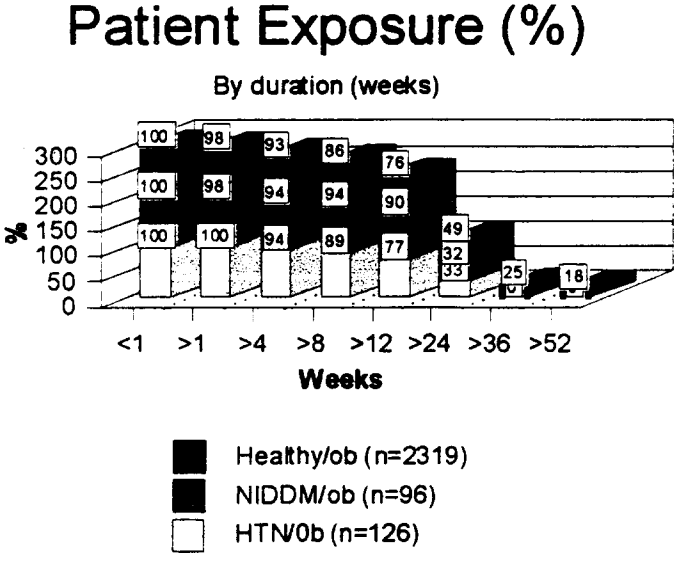
TABLE 10.1.2							
Study population	**< 5 mg**	**5-9 mg**	**10-14 mg**	**15-19 mg**	**20-29 mg**	**≥ 30 mg**	**All doses**
Obese	198	249	628	617	520	107	2319
Obese/HTN	0	0	116	0	10	0	126
Obese/NIDDM	0	0	1	84	11	0	96
All obese	198	249	745	701	541	107	2541
Depressed	22	307	460	404	12	3	1208

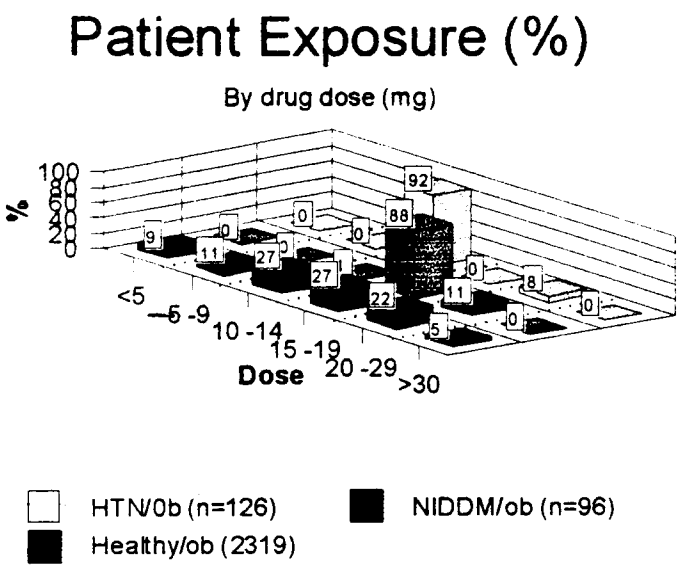
TABLE 10.1.2							
Study population	**< 5 mg**	**5-9 mg**	**10-14 mg**	**15-19 mg**	**20-29 mg**	**≥ 30 mg**	**All doses**
Volunteers	15	35	16	122	201	68	457
All subjects	235	591	1221	1227	754	178	4206

The below figure illustrates the percentage of subjects studied by patient population.



The below figures illustrate the percentage of healthy, hypertensive, and diabetic obese patients exposed to sibutramine by duration and dosage, respectively.





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The above data illustrate that the majority of the healthy obese subjects studied were taking 10-20 mg QD of sibutramine for an average of less than 24 weeks. In the obese hypertensive patients, over 90% of the subjects studied were taking 10-15 mg QD of sibutramine with an average exposure time of approximately 4-6 weeks. In the obese NIDDM patients, the vast majority were taking 15-20 mg of sibutramine, with an average exposure time of approximately 6 weeks.

Baseline demographics

The majority (80%) of the obese subjects studied were between the ages of_____, years, approximately 80% were female, and roughly 87% were Caucasian and 10% African-American. Only 1% of the subjects were over the age of 65 years. In general, the subjects in the hypertension and NIDDM studies were older and there were more males compared to the subjects in the healthy obese studies. The mean BMI of the sibutramine subjects was 33.8 kg/m^2. The majority of the subjects had an upper body distribution of fat as indicated by a mean waist to hip ratio of 1.0 and 0.8 for the men and women, respectively.

Premature discontinuations

In the placebo-controlled studies of all obese subjects, 10.2% of the sibutramine subjects and 8.4% of the placebo subjects withdrew because of an adverse event. Of the obese, hypertensive subjects 4.2% of the sibutramine subjects and 2.7% of the placebo subjects withdrew due to an adverse event. And of the obese diabetic subjects, 6.8% of the sibutramine subjects and 4.0% of the placebo subjects withdrew because of an adverse event.

Dose reductions due to adverse events

The majority of patients with dose reductions were from BPI 852. In this study, if a patient experienced either an intolerable adverse event, or had two mean supine pulse rates greater than 100 beats per minute, or a systolic blood pressure greater than 160 mmHg or a diastolic pressure greater than 95 mmHg, the patient's dose was reduced. Overall, 65 of 899 (7.2%) sibutramine-treated patients had their dose permanently reduced due to intolerable adverse events.

Table 10.1.7 provides the number of subjects at each dose who had a permanent dose reduction.

TABLE 10.1.7

	Placebo n=148	**1mg n=149**	**5mg n=151**	**10mg n=150**	**15mg n=152**	**20mg n=146**	**30mg n=151**
Adverse event	3	7	4	10	6	15	23
Blood pressure	5	1	1	4	6	5	13
Pulse rate	1	1	2	0	4	11	4
Other	0	1	6	3	4	1	3
Unknown	0	0	1	1	0	1	1
Total #	9	10	14	18	20	33	44
Percentage	**6%**	**7%**	**9%**	**12%**	**13%**	**23%**	**29%**

Clearly, more subjects in the 20 and 30 mg groups had permanent dose reductions because of an adverse event and there were significantly more dose reductions due to an increase in blood pressure in the 30 mg group.

The adverse events associated with permanent dose reductions included asthenia, headache, chest pain, hypertension, palpitations, tachycardia, anorexia, nausea, agitation, anxiety, dizziness, dry mouth, hyperkinesia, insomnia, nervousness, tremor, rash, and dyspnea. Of note,

10.2

10.2.1 Significant/Potentially Significant Adverse Events

The majority of the adverse event data are from studies in obese patients with an occasional reference to subjects from depression studies.

Cardiovascular adverse events

Table 10.2.1 illustrates the cardiovascular events that occurred more frequently in the sibutramine-treated patients compared to the placebo subjects.

TABLE 10.2.1		
Adverse event	**Sibutramine**	**Placebo**
Tachycardia	2.8%	0.5%
Palpitations	3.1%	1.2%
Hypertension	2.1%	0.8%
Vasodilatation	2.6%	0.8%

These events were also among those that most frequently led to premature termination of treatment in sibutramine-treated patients.

Of concern are the potential effects of sibutramine on cardiac conduction (i.e. arrhythmias). Sibutramine's inhibition of the reuptake of norepinephrine and resultant increase in sympathetic tone provide the pharmacological basis for this concern. The Knoll medical monitor determined that 31 last on-treatment ECGs from 2473 patients had clinically significant changes from their respective baseline ECGs. Twenty-eight of the 31 abnormalities were from subjects taking sibutramine and 3 were from placebo patients. The ratio of subjects taking sibutramine to those on placebo was 3.0, whereas, the ratio of clinically significant ECG changes in the sibutramine to placebo group was 9.0. The majority of these abnormalities were arrhythmias. A consultant cardiologist felt that 5 of the 28 ECGs represented clinically significant changes. These changes included frequent ventricular ectopic beats, atrial fibrillation, left bundle branch block, and T-wave changes. Although the precise number of subjects who had sibutramine-induced ECG abnormalities is difficult to determine with great precision, the drugs effect on pulse and blood pressure raise concern if the drug is taken by a large number of obese subjects, many of whom have occult coronary artery disease.

Dyspnea

In placebo-controlled studies involving obese and depressed patients, 29 sibutramine-treated patients (1.1%) reported dyspnea compared to one placebo-treated patient. One patient (#6015 from BPI 852X), a 54 year old Caucasian female was withdrawn from the study because of scleroderma and Raynaud's phenomenon. She had taken 20 mg QD of sibutramine for 24 weeks in BPI 852 and 15 mg QD for 14 weeks and then 20 mg QD for 14 weeks in BPI 852X. The scleroderma was diagnosed 10 weeks prior to her withdrawal. She experienced dyspnea 5 months prior to the diagnosis of scleroderma and felt to be secondary to pulmonary hypertension. A review of 22 case report forms from patients who complained of dyspnea revealed that 21 patients had spontaneous recovery of their shortness of breath. One subject was evaluated in an emergency room for her complaint of dyspnea. A complete cardiopulmonary

work-up was negative. This patient was eventually withdrawn from the study; her dyspnea resolved after she stopped the study medication. Of note, the majority of the cases of dyspnea occurred in subjects enrolled in depression studies.

An association between anorexic agents and primary pulmonary hypertension (PPH) was reported decades ago and the recently reported findings from the International Primary Pulmonary Hypertension Study confirm that the risk of developing primary pulmonary hypertension (PPH) is increased in individuals taking anorexigens for more than 3 months. It is not unreasonable to consider sibutramine as an anorexigen and as such, the risk for PPH may be increased with prolonged intake. This issue should be considered in the labeling if the NDA is approved.

CNS adverse events

Several CNS adverse events were recorded with a higher frequency in the sibutramine group compared to the placebo group. These included dry mouth, sweatiness, insomnia, and dizziness. In general, these symptoms were mild and not life-threatening. Three obese subjects (0.2%) treated with sibutramine in placebo-controlled studies reported seizure activity. One subject was diagnosed with a brain tumor, one subject had a history of epilepsy, and the third subject experienced a seizure-like event out of the hospital and a confirmed seizure while in the hospital. the relationship to the study medication (20 mg) was judged as possible. There were two reported cerebrovascular accidents and one report of a suspected subarachnoid hemorrhage. All subjects were female and taking 15 mg QD of sibutramine. The first subject had no history of hypertension and the event was recorded as possibly related to the study medication. The second subject was 52 years old and had a history of hypertension treated with medication. She received 15 weeks of drug treatment at the time of her stroke. Of note, her systolic blood pressure had increased 10 mmHg from baseline during the study without a change in the dose of her antihypertensive medication The third subject had a long history of hypertension controlled with amlodipine and atenolol. She did not have an increase in her blood pressure during the study and eventually completed the study on 15 mg QD of drug.

Acute interstitial nephritis

A 67 year old Caucasian female took 10 mg QD of sibutramine for 6 months in BPI 852 and then entered the open extension (BPI 852X) at daily doses of 15 mg for 4 weeks, increasing up to 20 mg for 4 weeks, 25 mg for 10 weeks, and 30 mg for 18 weeks. At the time of the event, the patient had been on 15 mg for approximately 2 weeks. She was withdrawn from the study because of increasing BUN and creatinine levels. A diagnosis of acute interstitial nephritis, possibly drug related was made on renal biopsy. The patient was treated with corticosteroids and underwent dialysis. Follow-up renal function evaluation showed complete recovery. The event was recorded as a probable drug-related event.

Thrombocytopenia

Four subjects (2 in depression studies) experienced thrombocytopenia during or shortly after discontinuation from a sibutramine study. A 61 year old female with depression took 5 mg of sibutramine for 2 weeks followed by 10 mg for 1 week and was found to have a platelet count of on routine laboratory examination. Her platelet count returned to normal within 3 weeks of the event. The event was recorded as probably related to sibutramine. In another depression study, a patient had an initial platelet count of , which decreased to after 12 days of treatment with 10 mg of sibutramine. The platelet count was 10 days after treatment was discontinued. No follow-up was available. A 39 year old male patient developed mild thrombocytopenia , 10 days after stopping sibutramine 10 mg. The patient did not return for 15 weeks at which time the platelet count had normalized The event was recorded as possibly related to the study drug. And the fourth subject experienced mild thrombocytopenia at the end of a 14-day treatment period with 20 mg of the drug. The platelet count returned to normal within 2 days of stopping the drug.

Ecchymosis and disorders of hemostasis

Serotonin is involved in platelet aggregation and in the regulation of blood vessel constriction and dilatation. Sibutramine inhibits the reuptake of serotonin and therefore it would not be unusual to find an increase in the incidence of ecchymosis or bruising with the use of this drug. Abnormal hemostasis has been reported with other drugs that inhibit the reuptake of serotonin such as fluoxetine and paroxetine. Treatment-emergent ecchymosis was reported in 1.2% of sibutramine-treated patients and in 0.2% of placebo patients. In seven of the 14 cases in placebo-controlled studies in obese patients, bruising occurred spontaneously and all the patients were females taking NSAIDs or aspirin. There was no associated decrease in platelet count. There was an excess of adverse events suggestive of abnormalities of hemostasis in patients treated with sibutramine in placebo-controlled studies compared to placebo subjects. These events were coded under the COSTART terms hemorrhage vaginal, GI, gum, rectal, eye, subarachnoid, hematuria, hemoptysis, ecchymosis, epistaxis, petechia, menorrhagia, and metrorrhagia.

Paresthesia/peripheral neuropathy

Paresthesia was reported by 52 sibutramine-treated patients (2.0%) compared to 7 placebo patients (0.7%). Tenosynovitis was reported by 23 sibutramine-treated patients (1.3%) and 2 placebo patients (0.3%). Many subjects had their symptoms categorized as carpal tunnel syndrome, however, review of these reports by the Sponsor indicated that in several cases the events may have represented a paresthesia. A 63 year old Caucasian male who received sibutramine 15 mg QD for one year developed paresthesias of the toes. He was subsequently diagnosed with early neuropathy on the basis of sensory deficits.

Pain and related adverse events

Pain events occurred more frequently in patients treated with sibutramine than with placebo. The

excess of treatment-emergent events was accounted for by back pain, pain in the thighs, legs or feet, generalized aches and pains, pains in the teeth and jaw, dysmenorrhea and abdominal pain. Many subjects reported headache. It is possible that sibutramine heightens the awareness of such events due to it effect on the autonomic nervous system. Headaches may be related to sibutramine's effects on cranial blood vessel reactivity, and dysmenorrhea due to effects on uterine muscle and blood vessels, both secondary to the inhibition of serotonin reuptake. The abdominal pain was frequently associated with either constipation or diarrhea, nausea or vomiting, indigestion, eructation or flatulence.

Infection and flu syndrome

Infection, and the possibly related adverse events such as laryngitis, pharyngitis, rhinitis, sinusitis, ear disease and flu syndrome, were more frequently reported treatment-emergent events in sibutramine-treated obese patients than in placebo-treated patients. Approximately 90% of the infections reported by sibutramine-treated patients were upper respiratory tract infections, including cold and cold symptoms. Sibutramine, like other SSRIs, appears to be associated with a "flu syndrome" and symptoms which could be described as flu-like (backache, myalgia, arthralgia, and headache).

Impotence and urinary retention

Impotence and urinary retention were observed primarily in the sibutramine-treated depressed patient population. In placebo-controlled studies of depressed patients, impotence was observed in 1.7% of sibutramine-treated patients and in 0.3% of the placebo patients. Urinary retention was observed in 1.1% of the sibutramine-treated patients and in no placebo subjects. In comparison, in sibutramine-treated obese patients the incidence of impotence and urinary retention were 0.2% and 0.1%, respectively for the active-drug group and no reports of either-symptom in the placebo subjects. The decreased reporting of impotence in the obesity studies may reflect the preponderance of female patients in these studies. Impotence and urinary retention have been reported with other serotonin and norepinephrine reuptake inhibitors, such as venlafaxine.

10.2.2 Deaths

There were 2 deaths by suicide in depression studies. There was one death in the obesity studies. This 37 year old Caucasian male had a history of coronary artery disease and hypertension and suffered a myocardial infarction 15 days after completing treatment with 10 mg QD of sibutramine for 12 weeks. The subject's completion ECG did not differ from his baseline tracing.

10.2.3 Overdose Exposure

An overdose exposure occurred in a 2 year old daughter of a study participant. This girl ingested up to eight 10 mg capsules of sibutramine. The child was observed in the hospital and did not

experience any complications. Telephone follow-up 5 weeks after the event confirmed that the child did not have any permanent sequela.

A 30 year-old male patient in a depression study attempted suicide by taking an overdose of his study medication along with alcohol. He ingested approximately 100 mg of sibutramine. The patient recovered without serious sequela. No laboratory or ECG abnormalities were noted.

10.3 Other Safety Findings

10.3.1 Adverse events

Adverse events occurring during the active-treatment period, within 6 days of discontinuing the study medication, or present at baseline but worsening during the course of the study were considered to be treatment-emergent.

Adverse drug incidence tables

The percentage of **all** obese patients reporting adverse events in placebo-controlled studies with an incidence of > 1% in the sibutramine group and the difference compared to placebo was statistically significant or near significant are shown in table 10.1.7

TABLE 10.3.1		
COSTART body system	**Placebo n=605**	**OSibutramine n=1766**
Infection	12.7	22.8
Abdominal pain	3.3	4.8
Vasodilatation	0.8	2.6
Tachycardia	0.3	2.5
Anorexia	4.3	14.1
Constipation	6.1	11.4
Appetite increase	2.8	9.3
Nausea	3.0	5.9
Tenosynovitis	0.3	1.3
Joint disorder	0.3	1.1
Dry mouth	4.8	18.2
Insomnia	4.6	10.8
Dizziness	3.6	7.3

TABLE 10.3.1		
COSTART body system	**Placebo n=605**	**OSibutramine n=1766**
Paresthesia	0.7	2.1
Dyspnea	0.0	1.0
Rhinitis	8.9	11.2
Sweat	0.7	2.5
Taste perversions	1.0	2.4
Ear disorders	0.5	2.0
Dysmenorrhea	1.0	3.5

O all doses combined

Adverse events that appeared to be dose-related include vasodilation, tachycardia, palpitations, anorexia, nausea, dry mouth, taste perversion, and possibly dyspnea.

Although no statistical analyses were provided by the Sponsor, the following tables provide the adverse events (% of subjects) that occurred in ≥ 2% of the obese hypertensive and diabetic populations and were numerical greater than the percentage in the placebo patients.

TABLE 10.3.2 OBESE HYPERTENSIVE PATIENTS		
COSTART term	**Sibutramine n=72**	**Placebo n=75**
Chills	2.8	0.0
Headache	11.1	6.7
Neck pain	2.8	0.0
Tachycardia	2.8	0.0
Constipation	13.9	9.3
Nausea	6.9	2.7
Dry mouth	16.7	2.7
Insomnia	5.6	0.0
Increased sweating	5.6	2.7
Urinary tract infection	2.8	0.0

TABLE 10.3.3 OBESE DIABETIC PATIENTS		
COSTART term	**Sibutramine n=59**	**Placebo n=50**
Infection	16.9	2.0
Malaise	3.4	2.0
Abdominal pain	8.5	4.0
Constipation	27.1	26.0
Dyspepsia	8.5	4.0
Nausea	10.2	4.0
Rectal disorder	3.4	0.0
Arthralgia	10.2	8.0
Joint disease	3.4	2.0
Dry mouth	18.6	10.0
Nervousness	3.4	2.0
Bronchitis	3.4	0.0
Pharyngitis	18.6	12.0
Sinusitis	3.4	0.0
Nail disorder	3.4	0.0
Increased sweating	11.9	4.0
Dysuria	3.4	0.0
Urinary tract infection	5.1	2.0
Urinary frequency	3.4	0.0

It is of interest to note that the incidence of infections is dramatically higher in the obese diabetic patients compared to the controls. The Sponsor states that the majority of the infections were classified as upper respiratory infections.

Time to onset of first report of an adverse event

Most adverse events in the obese population occurred either during the first 4 weeks of treatment, or occurred with a relatively even distribution throughout the treatment period. Dry mouth, anorexia, and insomnia were reported at a higher incidence in the first week, but the number of new reports decreased thereafter. Anxiety appeared to have occurred more frequently as the duration of treatment increased.

Duration of adverse events

Adverse events with a short duration (within 7 days) included nausea, dysmenorrhea, dizziness, palpitations, and abdominal pain. Adverse events with a longer duration (at least 15 days) included constipation, paresthesia, anxiety, sweating, anorexia, increased appetite, dry mouth, and taste perversion. It is important to known how many subjects dropped out of the study due to an adverse event early in the study, as this could affect the pattern of occurrence of adverse events.

Adverse event by total daily dose at the time of the event

The events that appeared to be dose-related included palpitations, tachycardia, vasodilatation, anorexia, nausea, dry mouth, taste perversion, insomnia, and nervousness.

Post-treatment adverse events

The most frequently reported post-treatment adverse event was headache. This adverse event was reported by 3.2% of sibutramine subjects compared to 0.3% of the placebo subjects.

Withdrawals due to an adverse event

In the placebo-controlled studies of obese patients, 9.9% of the sibutramine subjects and 8.4% of the placebo subjects were withdrawn due to an adverse event. More nervous system and cardiovascular system events led to withdrawals from sibutramine treatment compared to treatment with placebo. Table 10.3.4 illustrates the percentage of obese patients withdrawn from placebo-controlled studies due to adverse events with a sibutramine-withdrawal rate ≥ 0.5% and greater than the placebo-withdrawal rate.

TABLE 10.3.4

COSTART term	Placebo n=605	Sibutramine n=1766
Hypertension	0.3%	1.0%
Insomnia	0.3%	0.8%
Depression	0.5%	0.7%
Dizziness	0.3%	0.6%

10.3.2 Laboratory findings

Laboratory data are presented in 3 formats. First, the mean percentage change from baseline is presented for each dosage group as well as for all dosage groups combined. Second, shift tables

indicate the number of patients who had normal baseline values and shifted into the high or low ranges based on the normal ranges for that particular study and laboratory. And third, the absolute number and percentage of laboratory values considered clinically significant (neuropharmacology guidelines) are presented.

Hematology

Table 10.3.2.1 illustrates the mean percent change from baseline to the last observation in healthy obese subjects in placebo-controlled studies.

TABLE 10.3.2.1

	Placebo	**Sibutramine**
Hemoglobin	-0.4 (386)	-0.2 (1427
Hematocrit	-0.1 (386)	0.7 (1427)
RBC	0.7 (223)	-0.7 (535)
WBC	0.9 (386)	-2.0 (1426)
Neutrophils	1.1 (373)	-0.3 (1409)
Lymphocytes	2.5 (386)	3.5 (1426)
Monocytes	6.3 (373)	7.4 (1408)
Eosinophils	17.1 (373)	22.3 (1407)
Basophils	9.9 (368)	9.4 (1402)
Platelets	-1.7 (386)	1.9 (1425)

values in parentheses represent the number of patients

There was a greater percentage of sibutramine patients who had normal baseline WBCs with high on-treatment values compared to placebo-treated subjects (5.6% vs 3.5%, respectively). The Sponsor states that the majority of these high on-treatment values in the sibutramine group were isolated events and the last on-treatment value returned to within the normal range. Similarly, a larger percentage of sibutramine-treated patients with normal platelet counts at baseline had shifts to high on-treatment values compared to placebo (3.8% vs 1.6%, respectively). No patient had a platelet count above 700,000/mm^3.

Serum chemistry

Electrolytes

Table 10.3.2.2 illustrates the mean percentage change in electrolytes in uncomplicated obese patients in placebo-controlled studies.

TABLE 10.3.2.2		
Parameter	**Sibutramine**	**Placebo**
Sodium	-0.2 (390)	-0.2 (1444)
Chloride	-0.4 (389)	-0.6 (1443)
Potassium	0.8 (391)	-0.3 (1441)
Phosphate	2.4 (163)	0.1 (896)
Calcium	-0.1 (391)	-0.5 (1443)

values in parentheses represent the number of patients

There were 2.3% of the placebo group and 5.0% of the sibutramine-treated group that had normal baseline calcium levels with and on-treatment low value.

Uric acid

There was a possible dose-related effect of sibutramine on serum uric acid levels. The mean change from baseline to last recorded observation for healthy obese patients in placebo-controlled studies was 0.023% for the placebo group and -8.298% for the 30 mg sibutramine group. It is unlikely that these reductions in serum uric acid are clinically relevant.

Glucose

In placebo-controlled studies, the mean percentage change from baseline in plasma glucose was -1.1% (n=1443) in the sibutramine-treated group and 0.2 (391) in the placebo-treated group. There were no clinically significant differences between the sibutramine and placebo groups with respect to the percentage of patients who had clinically significant values (<50 mg/dl or >180 mg/dl). In a population of uncomplicated obese subjects, sibutramine did not appear to adversely affect glucose concentrations. The values presented by the Sponsor were a combination of fasting and non-fasting values.

Albumin and total protein

There were no clinically significant changes in albumin or total protein in sibutramine-treated patients.

Creatine kinase and creatine kinase MB

The mean percentage increase from baseline in creatine kinase in uncomplicated obese patients was 11.5% for the sibutramine-treated group and 2.9% for the placebo group. In addition, 3.9% of sibutramine-treated patients had values outside the upper limit of normal compared to 2.5% of

the placebo-treated subjects. None of the uncomplicated obese patients had clinically significant values while receiving treatment. The mean percentage change from baseline in CKMB values were similar for the sibutramine and placebo groups (-3.9% and -3.1%, respectively). The percentage of patients with shifts outside the normal range was also similar in the two groups. These changes do not appear to be clinically significant.

BUN and creatinine

The mean percentage change in BUN in the uncomplicated obese subjects was 1.3% for the sibutramine-treated group and 1.2% for the placebo-treated subjects. For creatinine, the mean percentage changes were 0.1% and -0.8% for the sibutramine and placebo subjects, respectively. For BUN and creatinine, the number of subjects with values that shifted outside of the normal range were similar in the sibutramine and placebo groups. Clinically significant values were seen in 0.4% or less of the sibutramine and placebo subjects.

Urinalysis

Six percent and 3% of sibutramine-treated patients had clinically significant changes in values for ketone and hemoglobin, respectively, compared with 3% and 0% in the placebo subjects. In addition, 4.3% of sibutramine-treated individuals and 2.2% of placebo subjects had clinically significant changes in values for protein in the urine.

Liver function tests (ALT, AST, GGT, Alk Phos, LDH, and bilirubin)

Abnormal liver function tests were reported as adverse events in 1.2% of sibutramine-treated patients in placebo-controlled obesity studies, compared to 0.5% in placebo subjects. In placebo-controlled depression studies, 0.9% of sibutramine-treated subjects had abnormal LFT's compared with 0.6% of placebo subjects.

Table 10.3.2.3 provides the mean percentage change from baseline in liver function tests in uncomplicated obese patients in placebo-controlled studies.

TABLE 10.3.2.3

Parameter	Placebo	Sibutramine
Bilirubin	15.9 (391)	10.4 (1442)
ALT	11.5 (390)	9.4 (1445)
AST	6.3 (389)	11.2 (1445)
GGT	0.8 (227)	-1.4 (546)
Alk Phos	-0.7 (391)	1.5 (1442)

TABLE 10.3.2.3		
Parameter	**Placebo**	**Sibutramine**
LDH	-0.9 (377)	-1.0 (1424)

values in parentheses represent the number of patients

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The only liver function test that was increased significantly when compared to the placebo group was AST (11.2% vs 6.3%, sibutramine vs placebo).

Table 10.3.2.4 illustrates the percentage of uncomplicated obese patients in placebo-controlled studies with an on-treatment value for liver function tests that exceeded the upper limit of normal.

TABLE 10.3.2.3		
Parameter	**Placebo**	**Sibutramine**
Bilirubin	1.6 (386)	2.3 (1421)
ALT	9.2 (349)	12.7 (1280)
AST	3.5 (367)	6.0 (1370)
GGT	3.8 (212)	2.7 (518)
Alk Phos	2.4 (379)	3.8 (1383)
LDH	4.8 (354)	5.2 (1378)

values in parentheses represent the number of patients

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The percentage of sibutramine-treated patients with clinically significant changes in laboratory values was < 0.5%. The data do not rule out the possibility of a drug-related increase in bilirubin, ALT, and in particular, AST.

Table 10.3.2.3[a] details the information associated with patient withdrawal from obesity and depression clinical studies because of an abnormal LFT value.

TABLE 10.3.2.3[a]						
Indication	**Sex**	**Age**	**Dose**	**Duration**	**Event**	**Comment**
Obesity	M	47	10mg	14 d	raised Alk Phos and GGT	raised at baseline and increased during trial
Depression	M	28	10mg	6 d	raised LDH, AST, and ALT	evidence of heavy ETOH use
Depression	M	33	10mg	5 d	elevated biliburin	screening was _ which increased to

TABLE 10.3.2.3[a]						
Indication	**Sex**	**Age**	**Dose**	**Duration**	**Event**	**Comment**
Obesity	?	?	15mg	163 d	raised GGT at baseline	further increases in GGT, AST, and ALT
Depression	?	?	10mg	100 d	raised AST and ALT	also taking tetracycline
Obesity	F	58	15mg	207	raised ALT and GGT	returned to normal 10 weeks post-treatment
Obesity	M	34	20-10mg	121 d	raised AST, ALT, and LDH	returned to normal 30 days post-treatment
Depression	F	44	10-20mg	42 d	raised Alk Phos, AST, and ALT	outcome ?
Depression	F	53	10-20mg	27 d	raised Alk Phos, AST, and ALT	resolved within 1 month

Thyroid function tests

There were no clinically significant changes from baseline in the values for the thyroid function tests in the sibutramine-treated subjects when compared to the control subjects.

Plasma lipoprotein lipids

The lipoprotein lipid data represent a combination of fasting and non-fasting samples; therefore, the accuracy of the measurements, particularly high density lipoprotein lipids and triglycerides are questionable.

Table 10.3.2.4 provides the mean percentage change from baseline to endpoint in plasma lipid levels in uncomplicated obese patients in placebo-controlled studies.

TABLE 10.3.2.4		
Parameter	**Placebo**	**Sibutramine**
Total cholesterol	-1.7 (360)	-3.4 (1297)
Triglyceride	0.2 (360)	-8.9 (1296)
LDL	-1.0 (121)	-4.2 (729)
HDL	-0.2 (133)	3.1 (749)

values in parentheses represent the number of patients

Vital signs

Table 10.3.2.5 provides the criteria for clinically significant (FDA Neuropharmacology guidelines) and borderline clinically significant (Sponsor's guidelines) abnormal vital signs. In order to be identified as clinically significantly abnormal, an on-drug value needed to meet the criterion value, and also represent a change of at least the magnitude noted in the change relative to baseline column. Baseline measurements were defined as those nearest in time prior to the first dose of study medication. Mean changes from baseline were calculated for subjects with baseline data and at least one on-therapy value.

TABLE 10.3.2.5

Criteria for Clinically Significant Abnormal Vital Signs

Variable	Criterion Value	Change relative to Baseline
Systolic BP (mmHg)	≥ 180	Increase of ≥ 20
	≤ 90	Decrease of ≥ 20
Diastolic BP (mmHg)	≥ 105	Increase of ≥ 15
	≤ 50	Decrease of ≥ 15
Heart rate (beats/min)	≥ 120	Increase of ≥ 15
	≤ 50	Decrease of ≥ 15
Criteria for Borderline Clinically Significant Abnormal Vital Signs		
Systolic BP (mmHg)	≥ 140	Increase of ≥ 10
	≤ 100	Decrease of ≥ 10
Diastolic BP (mmHg)	≥ 90	Increase of ≥10
	≤ 60	Decrease of ≥ 10
Heart rate (beats/min)	≥ 100	Increase of ≥ 10
	≤ 60	Decrease of ≥ 10

Blood pressure: Mean change from baseline.

Table 10.3.2.6 illustrates the mean change from baseline in systolic and diastolic blood pressure (mmHg) in uncomplicated obese patients in placebo-controlled studies by dose.

TABLE 10.3.2.6

Measurement	Placebo	< 5mg	5-9 mg	10-14 mg	15-19 mg	20-29 mg	≥ 30 mg	All doses
Resting SBP	-0.7	0.1	2.0*	1.0	2.7*	1.7*	4.0*	1.7*

TABLE 10.3.2.6								
Measurement	**Placebo**	**< 5mg**	**5-9 mg**	**10-14 mg**	**15-19 mg**	**20-29 mg**	**≥ 30 mg**	**All doses**
Standing SBP	0.9	1.2	1.1	3.1	3.3	3.5	1.2	2.3
Resting DBP	-0.6	-0.1	1.5*	1.4*	1.8*	2.2*	3.1*	1.5*
Standing DBP	0.5	-1.3	0.6	1.7	4.0*	2.6	2.3	1.7

* $p \leq 0.05$ compared to placebo

These data affirm that doses of 5 mg and higher are associated with elevations in blood pressure. It should be kept in mind that doses of 5 mg and above are associated with reductions in bodyweight, thus an increase in blood pressure is clearly an undesirable drug effect.

Following cessation of therapy (4 and 6 weeks) in the 6 and 12 month studies mean changes from baseline in systolic and diastolic blood pressure were elevated compared to baseline but were trending down.

Clinically significant and borderline clinically significant changes

Table 10.3.2.7 provides the percentage of patients with uncomplicated obesity in placebo-controlled studies with clinically significant and borderline clinically significant changes in systolic and diastolic blood pressure (mmHg).

TABLE 10.3.2.7				
CLINICALLY SIGNIFICANT CHANGES				
Measurement	**Direction**	**Position**	**Placebo**	**All doses**
Systolic BP	Increase	Resting	0.9%	1.0%
		Standing	0.0%	0.0%
Diastolic BP	Increase	Resting	0.2%	1.4%
		Standing	0.6%	1.2%
Systolic BP	Decrease	Resting	1.3%	2.0%
		Standing	2.6%	5.8%
Diastolic BP	Decrease	Resting	1.3%	0.6%
		Standing	1.3%	1.7%
BORDERLINE CLINICALLY SIGNIFICANT CHANGES				
Systolic BP	Increase	Resting	25.4%	26.2%
		Standing	11.6%	16.3%

BORDERLINE CLINICALLY SIGNIFICANT CHANGES				
Systolic BP	Increase	Resting	25.4%	26.2%
Diastolic BP	Increase	Resting	17.9%	21.7%
		Standing	16.8%	26.2%
Systolic BP	Decrease	Resting	13.9%	17.6%
		Standing	30.3%	32.4%
Diastolic BP	Decrease	Resting	13.4%	13.6%
		Standing	11.0%	13.4%

Heart rate: Mean change from baseline

Table 10.3.2.8 illustrates the mean change in heart rate (bpm) from baseline in uncomplicated obese patients in placebo-controlled studies.

TABLE 10.3.2.8								
Measurement	Placebo	<5mg	5-9mg	10-14mg	15-19mg	20-29mg	≥30mg	All doses
Resting HR	0.0	-0.1	2.9*	3.6*	3.9*	3.5*	5.1*	3.2*
Standing HR	-1.4	-1.2	1.7*	3.0*	2.9*	4.7*	5.0*	2.5*

* $p \leq 0.05$ compared to placebo

These data indicate that sibutramine is associated with an increase in pulse rate and the relationship is dose-related. The heart rate data obtained from ECGs were similar to that obtained by manual palpation, but the rates were, in general, 2-3 beats per minute higher.

As with blood pressure, at 4 and 6 weeks post-treatment the sibutramine subjects still had mildly, and dose-related elevations in heart rate.

Clinically significant and borderline clinically significant changes

Table 10.3.2.9 illustrates the percentage of patients with uncomplicated obesity from placebo-controlled studies with clinically significant or borderline clinically significant changes in heart rate.

TABLE 10.3.2.9				
CLINICALLY SIGNIFICANT CHANGES				
Measurement	**Position**	**Direction**	**Placebo**	**All doses**
Pulse rate	Resting	Increase	0.0%	0.3%
	Standing		0.0%	1.2%
—	Resting	Decrease	0.6%	0.9%
	Standing		0.0%	0.6%
BORDERLINE CLINICALLY SIGNIFICANT CHANGES				
Pulse rate	Resting	Increase	2.1%	5.4%
	Standing		7.7%	20.7%
	Resting	Decrease	16.2%	13.7%
	Standing		18.1%	14.0%

A greater percentage of sibutramine-treated patients reported an increase in heart rate or palpitations as an adverse event compared to placebo-treated patients (2.5% vs 0.3%, respectively for increase in heart rate and 2.3% vs 0.8%, respectively for palpitations).

Persistent hypertensive and tachycardic effects

Table 10.3.2.10 provides the percentage of patients whose vital signs met the borderline clinically significant criteria on three consecutive visits.

TABLE 10.3.2.10		
Parameter and position	**Placebo**	**All doses**
Systolic BP (mmHg)		
Resting	4.9%	5.7%
Standing	0.0%	1.5%
Diastolic BP (mmHg)		
Resting	1.5%	3.5%
Standing	0.0%	3.1%
Pulse rate (beats/min)		
Resting	0.0%	0.3%
Standing	0.0%	1.1%

One percent of sibutramine-treated subjects were withdrawn from studies because of increased blood pressure compared to 0.4% of placebo subjects. Regarding the number of subjects who were withdrawn because of an elevated pulse rate: 0.4% and 0.2% of sibutramine and placebo-treated subjects, respectively were discontinued prematurely. Similar numbers were found for palpitations: 0.3% and 0.0% of sibutramine and placebo subjects, respectively were withdrawn prematurely for an increase in pulse rate.

Table 10.3.2.11 shows the percentage of patients in BPI 852 who had dose reductions, by initial dose, because of increased blood pressure or pulse.

TABLE 10.3.2.11

Reason for dose reduction	**Placebo**	**1mg**	**5mg**	**10mg**	**15mg**	**20mg**	**30mg**
Blood pressure (mmHg)	3.4	0.7	0.7	2.7	3.9	3.4	8.5
Pulse (beats/min)	0.7	0.7	1.3	0.0	2.6	7.5	2.6

Criteria for discontinuation: two mean supine pulse rates > 100 beats/min, or systolic blood pressure > 160 mmHg or diastolic > 95 mmHg.

Undoubtedly, a larger number of subjects would have required dose reductions if the cuffoff values for systolic and diastolic blood pressure were 140 and 90 mmHg, respectively.

Electrocardiograms

In general, sibutramine-treated individuals had minor reductions in their PR and QRS intervals and increases in their QT_c intervals. These changes do not appear to be clinically significant.

The ECGs were categorized into one of three groups:

(1) Normal at baseline and on treatment.
(2) Abnormal at some stage during treatment but with the last recorded ECG either normal of no change from baseline.
(3) Normal at baseline with the last recorded ECG either abnormal or changed from baseline.

Eighty-five percent of the sibutamine and placebo ECGs were included in category 1. Approximately 10 % of the ECGs were included in category 2, and 4% were included in category 3. The ECGs from category 3 were reviewed by a Company medical monitor to determine whether the change following drug treatment was clinically significant. Thirty-one patients: 1.1% of the sibutramine-treated and 0.4% of the placebo-treated subjects were judged to have ECGs with a potentially clinically significant change from baseline. Of these 31 subjects, 28 received sibutramine and 3 placebo. A consulting cardiologist reviewed these 31 cases and determined that 5 of the 31 represented clinically significant changes and a drug-associated effect could not be ruled out. Of note, there were inconsistencies noted in the consultant

cardiologist's review of the EKGs. The Sponsor has been asked to address this issue. The response is pending.

10.3.3 Special Studies

Effects of alcohol and sibutramine

SB 2822

This was a double-blind, randomized, placebo-controlled, 4-way crossover study that investigated the psychomotor interactions between alcohol and 20 mg of sibutramine. The study participants were normal weigh, healthy male and female subjects, with a mean age of 27 years. Subjects received each of the following treatments:

1. Two placebo capsules and an alcoholic drink
2. Two sibutramine 10 mg capsules and a placebo drink
3. Two placebo capsules and a placebo drink
4. Two sibutramine 10 mg capsules and an alcoholic drink

The amount of alcohol in the drink was 0.5 g/kg of body weight diluted with 400 ml of ginger ale. The tasks that were performed at baseline and at 3, 4, 5, 6, and 10 hours after administration of the study capsules were:

1. Word presentation and immediate word recall
2. Picture presentation
3. Simple reaction time
4. Number vigilance
5. Choice reaction time
6. Visual tracking
7. Spatial memory
8. Memory scanning
9. Delayed word recall
10. Work recognition
11. Picture recognition
12. Body sway

Of the 156 summary measures of the psychomotor tasks, not surprisingly, 5% resulted in statistically significant sibutramine-by-alcohol interactions. These were confined to the word and picture recognition tasks.

The greatest percentage of reported adverse events were in the placebo plus alcohol group (80%) followed by the sibutramine plus alcohol (60%). There were no significant treatment effects on laboratory or vital sign parameters. It is of note to mention that the breath alcohol levels were 3.3 mg % lower with sibutramine treatment; the reason for this result is unknown.

In conclusion, in this small study of healthy young volunteers, 20 mg of sibutramine did not significantly alter the psychomotor response to a one-time ingestion of alcohol. The extremely large number of pairwise comparisons, without statistical correction, make it difficult to draw valid conclusions from this study.

Psychotrophic drug profile

BPI 802

In study BPI 802 12 healthy volunteers participated in a double-blind, single-dose crossover study in which the quantitative pharmacoelectroencephalographic effects of 5, 15, and 50 mg of sibutramine were compared to placebo and 50 mg of amitriptyline. Both 5 and 15 mg of sibutramine were categorized as antidepressants. The 50 mg dose was similar to CNS depressants, with secondary resemblance to cognitive activators.

Sleep effects

SSB 9045

In SSB 9045, the effect of 20 mg of sibutramine given once-daily in the morning for five days on sleep patterns and the distribution of rapid eye movements (REM) was investigated in 12 healthy volunteers. Similar to other antidepressants, sibutramine increased the time to onset of REM and decreased REM duration. There was also an increase in the time spent in Stage 1 of sleep.

Effect of sibutramine on cigarette usage

PSB 1898

This was a randomized, placebo-controlled, parallel-group study to examine the effects of 15 mg QD on the total number of cigarettes smoked and on the desire to smoke. The study had a baseline assessment week, a 2-week placebo run-in phase, and a 2-week double-blind treatment period. Twenty-four male subjects entered the run-in phase and all volunteers completed the study. There were no statistically significant differences in either the number of cigarettes smoked or the desire to smoke between the sibutramine and placebo groups. Similar adverse events were reported in the sibutramine and placebo groups, although the incidence of adverse events was higher in the sibutramine group than in the placebo group. There were no significant changes in body weight in either group.

Effect of sibutramine on the efficacy of the oral contraceptive pill

SB 4819

This was a single-blind, single-center study that compared the effects of 15 mg QD of sibutramine vs placebo on the efficacy of oral steroid contraceptives in 12 healthy female volunteers. The main variable measured was the change in plasma progesterone level. The study consisted of two study periods. In study period 1, all volunteers received placebo once-daily for 28 days (days -7 to 21) and their prescribed oral contraceptive for 21 days (days 1 to 21). Study period 2 started on day 22 and was the same as study period 1, with the exception that volunteers received sibutramine 15 mg QD instead of placebo. Eleven of 13 subjects completed the study; one dropped-out because of an adverse event (nausea and vomiting), and the other because of a protocol violation. There were no statistically significant differences between the sibutramine and placebo treatment periods for the change in plasma progesterone, FSH, and EE_2. The mean LH levels were 4.2 U/l in the placebo period and 4.7 U/l in the sibutramine period. This difference is not clinically significant. Headache was the most commonly reported event during both treatment periods.

Neurotoxicity

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See pharmacology review

No human data are presented on the potential for neurotoxicity. Animal data do not provide evidence that sibutramine depletes brain serotonin levels.

10.3.4 Drug-Demographic Interactions

Adverse events

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Age

The Sponsor did not provide an analysis of the effects of age on the incidence of adverse events.

Gender

Table 10.3.4.1 provides the percentage of adverse events thought to be sibutramine-related for all obese patients by gender. Sibutramine-related is defined as an adverse event occurring at a frequency $\geq$ 1%, and significantly ($p \leq 0.05$) or near-significantly ($p > 0.05$ and ≤ 0.1) more than with placebo.

TABLE 10.3.4.1

COSTART TERM	Male n=499	Female n=2541
Infection	28	24
Abdominal pain	4	5
Vasodilatation	0.4	4

TABLE 10.3.4.1		
COSTART TERM	Male n=499	Female n=2541
Tachycardia	2	3
Post-dose hypotension	0.8	0.3
Palpitations	2	2
Anorexia	13	16
Constipation	8	12
Appetite increase	8	12
Nausea	3	6
Joint disease	0.4	1
Tenosynovitis	1	2
Dry mouth	13	21
Insomnia	8	12
Dizziness	5	7
Paresthesia	1	2
Anxiety	5	8
Nervousness	6	6
Dyspnea	0.4	1
Rhinitis	11	15
Sweating	2	3
Taste perversion	2	2
Ear disorder	1	2
Dysmenorrhea	NA	5
Impotence	1	NA
Urinary retention	0.4	0

NA = not applicable

The rate of infection was slightly higher in males, whereas nausea and dry mouth were more commonly reported by females. The smaller number of male subjects must be taken into account when analyzing these data.

Race

Eighty-six percent of the patients studied were Caucasian; 10% were African-American; and 4% were Oriental. Thus, it is difficult to draw firm conclusions regarding differences in the incidence of adverse events among the three racial group. Nevertheless, Caucasians reported abdominal pain, dizziness, and dysmenorrhea less frequently and African-Americans reported

insomnia less frequently.

Laboratory values

Gender

There were no obvious differences in the changes in serum chemistry, hematology, thyroid function, or urinalysis values when analyzed by gender. Males tended to have more favorable changes in triglyceride and high density lipoprotein lipid values. In general, males tended to lose more weight for a given dose of sibutramine compared to females; this may explain their more favorable lipid response.

Race

The value for the mean percentage change in AST was higher in Caucasians than in African-Americans (12.5 vs 5.1%, respectively). Caucasians also had a greater reduction in triglycerides compared to African-Americans (-9.4 vs -1.7%, respectively). There were no other obvious differences between the two racial groups.

10.3.5 Drug-Disease Interactions

Hepatic disease

The effects of a single 15 mg dose of sibutramine were investigated in an open-label, parallel-group study of 12 patients with normal liver function and 12 with impaired hepatic function. The mean age of these Caucasian males was approximately 50 years. Hepatic impairment was judged moderate by the Child-Pugh classification. The overall sibutramine concentrations were no higher, nor were they sustained for a longer time in the hepatically impaired subjects. The bioavailability of the two main active metabolites, M_1 and M_2 was increased by 24% in the hepatically impaired subjects.

Renal disease

The Sponsor has not submitted pharmacokinetic data from patients with renal disease.

10.3.6 Drug-Drug Interactions

Cimetidine

In study SB 4820, 12 healthy volunteers (6 male and 6 female) received a single oral dose of 15 mg of sibutramine, followed by repeated twice-daily doses of cimetidine 400 mg for 7 days. And on day 10 of the study subjects took a 15 mg dose of sibutramine with a single 400 mg dose of cimetidine. For the active metabolites, M1 and M2, there were statistically significant

differences between the two treatments. For M1, C_{max} was 27% greater for the sibutramine/cimetidine treatment compared to sibutramine alone, whereas for M2, C_{max} was 18% smaller for the sibutramine/cimetidine treatment. The AUC for M1 was 35% greater for the sibutramine/cimetidine treatment. When the data for M1 and M2 were combined for C_{max} and AUC the difference between the two treatments was less than 8%.

Erythromycin

In study BPI 879, 12 obese patients received repeated, once-daily doses of sibutramine 20 mg for 7 days. This was followed by repeated once-daily doses of 20 mg of sibutramine plus repeated thrice-daily doses of erythromycin 500 mg for the next 7 days. The concomitant administration of sibutramine and erythromycin resulted in minor increases in steady-state plasma concentrations of active metabolite M2. In addition, there appeared to be an increase in pulse when subjects were administered the two drugs together.

Ketoconazole

In study BPI 880, 12 obese patients received once-daily doses of sibutramine 20 mg for 7 days. This was followed by repeated once-daily doses of sibutramine 20 mg plus repeated twice-daily doses of ketoconazole 200 mg for 7 days. The concomitant administration of these two drugs increased the concentrations of active metabolites M1 and M2 and increased heart rate.

The results of the aforementioned studies suggest that patients should be monitored closely when taking sibutramine with either cimetidine, erythromycin, or ketoconazole as well as other similarly metabolized drugs.

10.3.7 Withdrawal Phenomena/Abuse Potential

The most frequently reported post-treatment adverse event was headache. Of note, a 42 year old female Caucasian patient had an acute psychotic episode two days after being discontinued from study BPI 872. She was admitted to the hospital and treated with antipsychotic agents. The episode resolved within 5 days of treatment.

It is interesting to note that the drug Effexor, an antidepressant with similar pharmacological actions to that of sibutramine has been associated with a withdrawal syndrome during post-marketing spontaneous reporting. Headache is a component of the withdrawal syndrome of Effexor, and is the most commonly reported symptom following discontinuation of sibutramine.

Study BPI 863 was conducted to evaluate the abuse potential of sibutramine (20 and 30 mg) compared to placebo and dextroamphetamine (20 and 30 mg). The Addiction Research Center Inventory (ARCI) was administered pre-dose and hourly for 4 hours after the administration of the medications. For stimulation and euphoria, dextroamphetamine was significantly greater than placebo, whereas, the effects of sibutramine were indistinguishable from placebo. For scales

measuring dysphoria, both doses of dextroamphetamine and 30 mg of sibutramine produced greater responses when compared to placebo. The 20 mg sibutramine dose was the same as placebo. The rank order of treatment session enjoyment was dextroamphetamine 30 mg > dextroamphetamine 20 mg > placebo > sibutramine 30 mg > sibutramine 20 mg.

10.3.8 Human Reproductive Data

Five patients became pregnant while taking sibutramine. These cases are summarized in table 10.3.8.1

TABLE 10.3.8.1

Patient #	Age	Dose	Duration	Outcome
1067	?	15mg	?	ectopic pregnancy; laparotomy and salpingectomy
0192	21	20mg	9 wk	pregnancy was therapeutically terminated
3150	?	15mg	2-3wks	normal child born
0424	22	15mg	19days	normal child born
464	?	15mg	8wk	neonate had seizures; dx with viral meningitis

10.4 SAFETY UPDATE

The Sponsor submitted a safety update on 12/19/95. This update includes five new studies and data from BPI 852X. The cutoff date for these data is 5/31/95. The five new studies are described in table 10.4.1

TABLE 10.4.1

Placebo-controlled Uncomplicated obese patients		Dose range	Number Exposed	Planned Duration	Age Range
BPI 858 Metabolic study	Parallel group double-blind	Sibutramine 10-30mg	33 Sib 16 Pl	8 wks	
BPI 864 Feeding behavior study	Crossover double-blind	Sibutramine 10-30mg	15 Sib 12 Pl	12 wks	
Uncontrolled					
Uncomplicated obese patients					
BPI 872 Holter study	Single-treatment single-blind	Sibutramine 5-30mg	21	10 wks	
Volunteers					

TABLE 10.4.1					
Placebo-controlled Uncomplicated obese patients		Dose range	Number Exposed	Planned Duration	Age Range
BPI 870 Renal impairment study	Single-treatment open-label	Sibutramine 15mg	6	1 day	
BPI 871 Bioequivalence study	Crossover Open-label	Sibutramine 30mg	28	4 days	

The data from these five studies have been combined an analyzed in a separate database. The data from BPI 852X have been combined with the previously reviewed data included in the ISS.

10.4.1 Overall Exposure

There have been a total of 2388 sibutramine exposures in patients with uncomplicated obesity as of the cutoff date of this update. Four-hundred-thirty-one patients received sibutramine for a duration of at least one year. At the time of the cutoff date, one patient in 852X had completed 102 weeks of sibutramine therapy.

10.4.2 Adverse Events

The most commonly reported adverse events in the five new studies were headache, anorexia, dry mouth, insomnia, increased appetite, dysmenorrhea, rhinitis, infection, nausea, CNS stimulation, and asthenia. These adverse events are representative of those reported in the integrated summary of safety (ISS).

Because of the small number of subjects in the five new studies and the differences in dose, duration, and monitoring of the patients, the remainder of this review will focus on data from BPI 852X, the long-term, open-label extension of the pivotal study BPI 852. In BPI 852X, 70% of the patients have withdrawn as of 5/31/95. Seventeen percent withdrew because of an adverse event and approximately 29% have withdrawn because of protocol violations.

The most commonly reported adverse events (incidence $\geq$10%) were headache, infection, anorexia, rhinitis, dry mouth, increased appetite, anxiety, flu syndrome, pain, sinusitis, back pain, injury accident, insomnia, arthralgia, and pharyngitis. Overall, the incidence of these adverse events were very similar to those reported in the ISS.

Withdrawals due to Adverse Events

Table 10.4.2.1 provides the number and percentage of patients in BPI 852X who were withdrawn due to a treatment-emergent adverse events with a withdrawal rate of $\geq$ 0.5%.

TABLE 10.4.2.1	
COSTART term	**number and (%) of patients n=572**
Hypertension	18 (3.2)
Depression	13 (2.3)
Headache	11 (1.9)
Insomnia	8 (1.4)
Anxiety	4 (0.7)
Dry mouth	3 (0.5)
Emotional liability	3 (0.5)
Nervousness	3 (0.5)
Chest pain	3 (0.5)

Clinically Significant Adverse Events

A 26 year old male patient in BPI 852X had received sibutramine 15-25 mg for approximately 10 months when he developed fever, nausea, vomiting and a rash. His platelet count upon admission to the hospital was , followed by a drop to 8 hours later. He also had abnormal liver function tests. Sibutramine was discontinued and his platelet count returned to normal at the time of discharge. He was diagnosed with viral illness. After 4 months, the patient resumed sibutramine at doses of 20-25 mg with no further laboratory abnormalities.

A 53 year old female in study 852X was diagnosed with possible retinal melanoma after receiving sibutramine 15-30 mg for 9 months. The patient has refused to confirm the diagnosis.

10.4.3 Laboratory Parameters

Because of the relatively small sample sizes in this update, only those individuals with clinically significant changes in laboratory parameters are reported. The following data are from the five new studies as well as from 852X.

Table 10.4.3.1 provides the number of patients with clinically significant abnormal laboratory parameters with an incidence of approximately 1.0%.

TABLE 10.4.3.1	
Parameter	**Number of patients**
Hct < 32% females	11/487
TSH > 7.5 uIU/ml	2/234
TG > 250 mg/dl*	81/565
Total cholesterol > 300 mg/dl	28/565
HDL-C < 25 mg/dl	17/565
LDL-C > 160 mg/dl	244/565
Eosinophils > 10%	5/588
ALT > 3X ULN	5/591

* lipid values are non-fasting

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10.4.4. Vital Signs and Electrocardiograms

Blood Pressure

The mean changes in blood pressure (mmHg) from baseline to 6, 12, and 18 months for subjects in 852X are shown in table 10.4.4.1

TABLE 10.4.4.1					
	Sibutramine - modal dose✤				
Systolic BP	15 mg	20 mg	25 mg	30 mg	All Doses
month 6	6.7(91)	7.1(90)	8.4(86)	5.0(157)	6.5(439)
month 12	6.2(58)	6.6(55)	6.8(63)	6.1(131)	6.1(318)
month 18	5.9(36)	10.8(35)	7.2(38)	7.8(93)	7.6(210)
Diastolic BP	15 mg	20 mg	25 mg	30 mg	All Doses
month 6	2.7(91)	4.4(90)	3.3(86)	2.0(157)	3.0(439)
month 12	1.8(58)	3.1(55)	2.2(63)	1.3(131)	1.8(318)
month 18	5.3(36)	8.4(35)	2.7(38)	3.0(93)	4.2(210)

✤modal dose represents the dose taken most frequently.
Numbers in parentheses represent the number of patients.

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An important issue related to blood pressure is the number of subjects with sustained increases in

blood pressure. Using the same criteria as defined in the ISS review, table 10.4.4.2 provides the number and percentage of subjects in 852X with sustained (3 consecutive visits) increases in systolic or diastolic blood pressure.

TABLE 10.4.4.2					
Measurement	**15 mg n=140**	**20 mg n=128**	**25 mg n=104**	**30 mg n=167**	**All Doses**
Systolic BP	6 (4%)	6 (5%)	7 (7%)	13 (8%)	35 (6%)
Diastolic BP	6 (4%)	4 (3%)	4 (4%)	5 (3%)	20 (4%)

dose represent modal dose
n = number of patients with at least three consecutive visits

Table 10.4.4.3 provides the percentage of patients in 852X with an increase in resting blood pressure ≥ 30% from baseline to endpoint and months 6, 12, and 18.

TABLE 10.4.4.3				
	Sibutramine modal dose			
	15 mg	**20 mg**	**25 mg**	**30 mg**
Systolic BP				
Endpoint	3%	5%	4%	3%
Month 6	0%	6%	4%	3%
Month 12	0%	0%	5%	4%
Month 18	0%	3%	5%	8%
Diastolic BP				
Endpoint	3%	6%	5%	2%
Month 6	1%	9%	1%	3%
Month 12	2%	4%	5%	2%
Month 18	6%	9%	5%	2%

Pulse rate

The mean change in pulse rate from baseline to months 6, 12, and 18 in the subjects from 852X are shown in table 10.4.4.4

TABLE 10.4.4.4					
Resting pulse	**15 mg**	**20 mg**	**25 mg**	**30 mg**	**All Doses**
month 6	5.4 (91)	6.4 (90)	8.1 (86)	7.2 (157)	6.7 (439)
month 12	4.7 (58)	8.4 (55)	8.0 (63)	7.8 (131)	7.1 (318)
month 18	8.4 (36)	7.8 (35)	7.6 (38)	6.9 (93)	7.2 (210)

dose represents the modal dose; values in parentheses are the number of subjects.

There were no subjects with a sustained elevation in supine pulse rate as defined by an increase in pulse rate of ≥ 100 bpm and an increase of ≥ 10 bpm above baseline. The Sponsor did not provide the data for resting or standing pulse.

Increases in resting pulse rate of ≥ 30% from baseline were observed in approximately 8-12% of the patients receiving modal doses of 15 mg or higher.

Electrocardiograms

In BPI 852X, the mean changes in heart rate from baseline to months 6, 12, and 18 as determined from ECGs were of a slightly greater magnitude than the changes noted by manual palpation. A dose-response relationship was also observed with modal doses of 15 mg and higher.

Safety update - 4/19/96

Two 10-day safety reports were submitted on 4/19/96. The first report was about a 65 year old female with a history of hypertensive cardiomyopathy and dyslipidemia, who was receiving 10-20 mg QD of sibutramine for one year and developed an intracerebellar hemorrhage. The patient's blood pressure, 220/110 on admission to the hospital was stabilized and she was discharged on a thiazide diuretic in addition to her captopril.The second report was about a 63 year old female with a history of asthma who was receiving 15 mg QD of sibutramine for 24 weeks. The patient developed sudden onset of palpitations and upon admission to the hospital had a heart rate of 150 bpm and a blood pressure of 160/100 mmHg. She was diagnosed with supraventricular tachycardia (SVT) and treated with verapamil. The cardiac work-up was normal. Of note: The patient's heart rate had increased by 13 bpm by the 20th week of treatment.

To date, there have been eight reported cerebrovascular accidents: Seven of these subjects were taking sibutramine and one was receiving placebo.

Summary of Safety

The data submitted in the integrated summary of safety and the safety update of 12/19/95 indicate that the common symptom-related adverse events associated with the use of sibutramine

(i.e. dry mouth, insomnia, nausea, etc) are, in general, not serious and reflect the pharmacodynamic actions of an inhibitor of serotonin and norepinephrine reuptake. However, the safety data indicate a possible to probable drug-related risk for several serious adverse events: cardiac arrhythmia, cerebrovascular accident, acute interstitial nephritis, thrombocytopenia, and bleeding disorders. Furthermore, the safety data highlight the paradoxical increase in blood pressure despite weight loss in sibutramine-treated patients.

11. DISCUSSION/CONCLUSIONS

The rationale for the treatment of obesity derives from the relationship between an excess level of body fat with numerous co-morbid conditions — the most common being hypertension,[1-4] non-insulin dependent diabetes mellitus,[5-9] and dyslipidemia.[10-14] The improvements in the major co-morbidities following the non-pharmacological treatment of obesity are well documented.[15-26]

As defined in the Guidance for the Clinical Evaluation of Weight-Control Drugs, an anti-obesity drug is considered efficacious if it is shown — after one year of treatment — to produce a mean percent loss of body weight that is 5% greater than the mean percent loss in the placebo group and the difference is statistically significant. Alternatively, a drug will be considered effective if the proportion of subjects who lose 5% of initial body weight is greater in the drug-treated group than the proportion in the placebo-treated subjects.

In the one-year pivotal study SB 1047, subjects were randomized to once-daily doses of 10 or 15 mg of sibutramine or to placebo. Less than 60% of the subjects randomized to each group completed the trial. Of these individuals, 65% of the subjects in the 15 mg group and 56% of the subjects in the 10 mg group lost 5% of initial body weight compared to 29% of placebo-treated subjects. However, only the 15 mg dose led to a mean percent weight loss that was 5% greater than the mean percent loss in the placebo group. The six-month dose-ranging study, BPI 852, reported that compared to placebo subjects, a greater percentage of subjects taking 5-30 mg QD of sibutramine lost 5% of initial body weight. On the other hand, only doses of 15-30 mg QD led to a percent weight loss that was 5% greater than the weight loss in the placebo group. The dose-response curve generated from BPI 852 suggests that weight loss is dose-dependent, with the steepest portion of the curve between the doses 5-20 mg.

Sibutramine's most worrisome safety issue centers on its effects on the major obesity-related co-morbidities, particularly blood pressure. A disturbing result of the dose-ranging study BPI 852, and its open-label extension 852X, was the paradoxical increase in blood pressure despite weight loss. Although the subjects in BPI 852 and 852X were normotensive at baseline, one would expect a reduction in blood pressure following weight loss in obese individuals.[27,28] In study SB 1047 a similar inverse relationship, albeit of a lesser magnitude, was observed between weight loss and blood pressure. In BPI 855, an eight-week study of obese, hypertensive patients taking 20 mg QD of sibutramine, a 1.7 kg reduction in body weight was associated with mean increases in systolic and diastolic blood pressures of approximately 9.0 and 4.0 mmHg, respectively. These changes were measured by 24-hour ambulatory monitoring — a measure of average daily blood pressure that correlates more closely with end-organ damage than manually-measured blood pressures[29,30] — and indicated that the overall increase in 24-hour blood pressure was due, in large part, to elevations in nocturnal pressures. In contrast to the results of the aforementioned studies, SB 3069, a six-month trial (three-months placebo-controlled and three-months open-label) of obese, hypertensive patients taking 10 mg QD of sibutramine, reported weight-loss

induced reductions in blood pressure. However, despite greater weight loss in the sibutramine group, the reductions in blood pressure were the same in the drug-treated and placebo patients. Moreover, there was no correlation between sibutramine-induced weight loss and a reduction in blood pressure following six months of drug treatment.

Given that small, sustained increases in blood pressure, even when within the normotensive range, are associated with an increased risk for cardiovascular disease,[31] the pressor effect of sibutramine is a significant safety concern. Furthermore, it is important to note that sibutramine's pressor effect does not appear to be dose-dependent. Consequently, restricting approval to the lower doses would not eliminate the potential for drug-induced increases in blood pressure.

Sibutramine was ineffective in the treatment of obese patients with non-insulin dependent diabetes mellitus. Six months of treatment with 15 mg QD resulted in only a 3.8% reduction in body weight. More importantly, the weight loss was associated with an increase in diastolic blood pressure, pulse, and post-load insulin levels, with no change in fasting glucose or $HbA1_c$ concentrations. In short, sibutramine worsened the risk factor profile of obese, non-insulin dependent diabetic patients.

With respect to lipoprotein lipids, in the one-year study SB1047, there were no statistically significant differences in the levels of total cholesterol or triglyceride between the drug-treated and the placebo-treated subjects at the completion of the trial. Pooled data from short and long-term studies suggest that sibutramine has a weak eulipemic effect. However, the Sponsor did not provide a statistical analysis of the pooled data, and therefore no valid conclusions can be made regarding the effect of sibutramine on lipoprotein lipid levels.

In summary, the 10 and 15 mg doses of sibutramine satisfy the minimum weight-loss criteria and duration of study as defined in the Guidance. However, sibutramine does not improve, and in some cases it aggravates, the major obesity-related co-morbidities.

13. RECOMMENDATIONS

13.1 As discussed above, sibutramine has an unsatisfactory risk - benefit ratio, and therefore this Reviewer recommends non-approval of the original submission of NDA 20-632.

5/10/96

Eric Colman, M.D.
Medical Officer

Concurrent Review

cc: NDA Arch
Drs.GTroendle/SSobel

6-25-96

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MEDICAL REVIEW of SAFETY UPDATE

NDA #: 20-632

SPONSOR: Knoll

NOV 14 1997

DRUG: Sibutramine

DATE SUBMITTED: 10/20/97

DATE RECEIVED, M.O.: 10/25/97

DATE OF REVIEW: 11/5/97

INTRODUCTION

This sibutramine safety update includes 11 studies which completed or had database lock since the second ISS was submitted in 2/97. Serious adverse events in ongoing studies reported to Knoll's safety group are current as of 9/1/97.

The 11 studies summarized in this report are as follows:

BPI 873 - Single dose effects of renal dysfunction on the PK of sibutramine.

BPI 881 - Effects of 12 weeks of 20mg qd of sibutramine on weight, BP, and pulse in patients with hypertension controlled with a beta-blocker, with or without concomitant diuretic therapy.

BPI 883 - Single dose effects of sibutramine (25 to 75 mg) on abuse potential compared with dextroamphetamine in diagnosed substance abusers.

BPI 893 - Single dose effects of sibutramine (25 to 75 mg) on abuse potential compared with dextroamphetamine and placebo in recreational stimulant users.

SB 4070 - 12-week study of the effects of 15 mg qd of sibutramine in the treatment of obese patients with dyslipidemia.

SB 4072 - 24-week study of the effects of 15mg qd of sibutramine on weight reduction in obese patients at risk for diabetes.

SB 5076 - A single dose study of 30mg qd of sibutramine examining the effect on energy expenditure in normal males.

SB 5079 - A single dose study of 15mg qd of sibutramine examining the effects on food intake and

hunger in normal males.

SB 5081 - A four-day treatment study of 10mg qd of sibutramine examining the effects on thermogenesis in obese patients.

SB 5083 - A 12-week study of 15 or 20mg qd of sibutramine examining the effects on heart rate variability in obese patients.

SB 5084 - An 8-week study of 15 mg qd of sibutramine examining the effects on energy expenditure in obese patients.

EXPOSURE

Of the studies listed above, 394 patients have received sibutramine and 328 placebo. Including the entire database, a total of 4273 patients (73 patient-years) have been exposed to sibutramine as of 9/1/97.

DEMOGRAPHICS

The majority of patients were female, the mean age ranges were from years, and of the subjects in the various studies were Caucasian.

PREMATURE TERMINATIONS

Sixteen percent of sibutramine-treated patients and 18% of placebo-treated patients have terminated early. Adverse events were the reason for early withdrawal in 5.2% of sibutramine-treated subjects and 2.7% of placebo-treated patients.

ADVERSE EVENTS

Adverse events that were recorded by a greater percentage of sibutramine- vs. placebo-treated patients and the differences were statistically significant include headache, palpitations, constipation, nausea, dry mouth, insomnia, and taste perversion.

Hypertension was reported as an adverse event in 1.0% of sibutramine-treated subjects vs. 1.2% of placebo-treated women. Tachycardia was reported as an adverse event in 2.3% and 0.4% of sibutramine- and placebo-treated patients, respectively.

DEATHS

No deaths have been reported in subjects receiving sibutramine.

OVERDOSE

A 45-year-old male was withdrawn after taking an overdose of diazepam on 8/12/97. He was started

on fluoxetine and lorazepam on 8/15/97. On the evening of 8/21/97, the patient took an overdose of sibutramine (20 x 20mg). He was hospitalized with a heart rate of 120bpm and was discharged the next day. Follow-up 19 days later indicated that he was clinically well.

VITAL SIGNS

Relative to placebo, sibutramine treatment increased mean systolic blood pressure by 3.2 mmHg, increased diastolic blood pressure by 3.8 mmHg, and increased pulse rate by 5.4 bpm. In general, more sibutramine-treated patients compared with placebo-treated subjects had increases in systolic and diastolic blood pressure and pulse that were of borderline clinical significance (e.g., diastolic BP >90 mmHg and an increase of > 10 mmHg from baseline). Most of the exposures to sibutramine were with the 15-20mg qd doses. As reported in the previous safety update, the most consistent finding is the increase in resting pulse rate in sibutramine-treated subjects.

MEDICAL OFFICER'S CONCLUSIONS

The data reported in this safety update are consistent with the findings from previous reports and indicate that the drug, particularly at doses greater than 15 mg qd, increases blood pressure and pulse.

11/13/97

Eric Colman, M.D.

cc: NDA Arch

11-14-97

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MEDICAL REVIEW

NDA #: 20-632

SPONSOR: Knoll

DRUG: Sibutramine

INDICATION: Weight loss

SUBJECT OF REVIEW: Safety update

DATE SUBMITTED: 10/4/96

DATE RECEIVED, M.O.: 10/9/96

DATE OF REVIEW: 10/10/96

BACKGROUND

This safety update includes data from 3 studies completed since the last safety update - December, 1995 - and represent data collected up to June 1, 1996. The studies are: SB 1049, SB 2056, and SB 2059. I reviewed the preliminary study reports for SB 1049 and SB 2059 in July, 1996.

A total of 254 subjects were randomized to sibutramine (10 mg qd) and 251 subjects were randomized to placebo in these 3 studies. The estimated patient years of exposure to sibutramine from these 3 studies is 120. The demographic characteristics of these patients reflect the demographic characteristics of the previously exposed patients: primarily middle-aged, Caucasian women with a mean BMI of $\approx$ 35.0 kg/m^2.

ADVERSE EVENTS

In general, the adverse event profiles in these 3 studies were similar to the adverse events most commonly reported in the Integrated Summary of Safety (ISS) and do not represent serious conditions. The table below shows the adverse events that were reported with an incidence of > 1% and the difference between active and placebo-treated patients was statistically or nearly statistically significantly different.

COSTART TERM	Sibutramine	Placebo	p value
Syncope	1.2%	0%	0.08
Constipation	12%	5%	0.005
Rectal disorder	3%	0.4%	0.02

COSTART TERM	Sibutramine	Placebo	p value
Dry mouth	9%	3%	0.009
Furunculosis	1.2%	0%	0.09

The most frequent adverse event that led to premature discontinuation was depression in 0.8% of the Sibutramine-treated patients.

SERIOUS ADVERSE EVENTS

Four Sibutramine-treated patients experienced serious adverse events during the time period 12/1/95 - 8/31/96 that were submitted as 10-day safety reports. One subject had a cerebrovascular disease of possible embolic origin; one subject had an intra cerebellar hemorrhage; one subject was diagnosed with a supraventricular tachycardia; and one subject complained of several neurological symptoms: paresthesia, dizziness, tremor, and visual blurring.

VITAL SIGNS

There were no statistically significant differences in the changes in systolic or diastolic blood pressure between the drug or placebo-treated patients. The change in pulse rate from Baseline to Endpoint was 1.7 in the Sibutramine group and -1.8 in the placebo subjects ($p<0.01$).

CONCLUSIONS

The data from the 3 studies included in this safety update are consistent with the findings reported in the ISS. No new safety issues appear to have emerged from these studies which included subjects taking 10 mg qd of Sibutramine.

10/11/96

Eric Colman, M.D.

cc: NDA Arch 10-11-96
Hess/Colman/Troendle

Please refer to pages 154-160 of Medical Officer's Review for safety update that was submitted 12/19/95.

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